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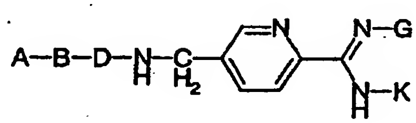
(54) PROMEDICAMENTS D'INHIBITEURS DE LA THROMBINE
(54) PRODRUGS OF THROMBIN INHIBITORS

(57)
The present invention relates to prodrugs of general formula (I). The meaning of said formula is given in the description. Disclosed are the prodrugs of pharmaceutically active, heterocyclic amidines. In vivo compounds which are competitive inhibitors of trypsin-like serine proteases, especially thrombin, are produced from the amidines. The invention also relates to the production and use of the prodrugs as medicaments.



(I)

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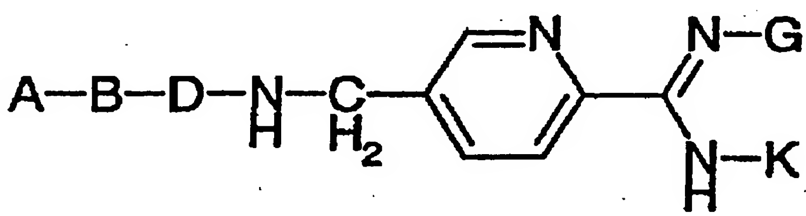
(54) Titre : PROMEDICAMENTS D'INHIBITEURS DE LA THROMBINE
(54) Title: PRODRUGS OF THROMBIN INHIBITORS



(I)

(57) Abrégé/Abstract:
The present invention relates to prodrugs of general formula (I). The meaning of said formula is given in the description. Disclosed are the prodrugs of pharmaceutically active, heterocyclic amidines. In vivo compounds which are competitive inhibitors of trypsin-like serine proteases, especially thrombin, are produced from the amidines. The invention also relates to the production and use of the prodrugs as medicaments.

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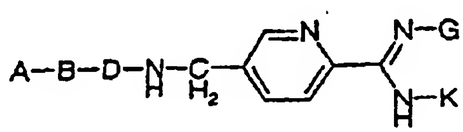
(54) Title: PRODRUGS OF THROMBIN INHIBITORS

(54) Bezeichnung: PRODRUGS VON THROMBININHIBITOREN



(I)

(57) Abstract

The present invention relates to prodrugs of general formula (I). The meaning of said formula is given in the description. Disclosed are the prodrugs of pharmaceutically active, heterocyclic amidines. In vivo compounds which are competitive inhibitors of trypsin-like serine proteases, especially thrombin, are produced from the amidines. The invention also relates to the production and use of the prodrugs as medicaments.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft Prodrugs der allgemeinen Formel (I), deren Bedeutung in der Beschreibung angegeben ist. Diese Prodrugs von pharmakologisch wirksamen, heterocyclischen Amidinen, aus denen in vivo Verbindungen entstehen, welche kompetitive Inhibitoren von Trypsin-ähnlichen Serinproteasen, besonders Thrombin sind, ihre Herstellung und ihre Verwendung als Medikamente, werden beschrieben.

Prodrugs of thrombin inhibitors

The present invention relates to prodrugs of pharmacologically active heterocyclic amidines, from which in vivo compounds result which are competitive inhibitors of trypsin-like serine proteases, particularly thrombin, their preparation and their use as medicaments. The invention also relates to pharmaceutical compositions which contain the prodrugs of the active compounds as constituents, and to the use of the compounds as thrombin inhibitors, anticoagulants and as antiinflammatory agents.

Thrombin belongs to the serine proteases group and plays a central role as a terminal enzyme in the blood-clotting cascade. Both the intrinsic and the extrinsic clotting cascades lead, via a number of amplification stages, to the formation of thrombin from prothrombin. The thrombin-catalyzed cleavage of fibrinogin to fibrin then initiates blood clotting and the aggregation of the platelets, which for their parts increase the formation of thrombin by means of the binding of platelet factor 3 and clotting factor XIII and also a whole series of highly active mediators.

Thrombin formation and action are central events in the genesis both of white, arterial thrombi and of red, venous thrombi and are therefore potentially effective points of attack for pharmaceuticals. In contrast to heparin, thrombin inhibitors are able, independently of cofactors, simultaneously to completely inhibit the actions of free thrombin and thrombin bound to platelets. In the acute phase, they can prevent thromboembolic events after percutaneous transluminal coronary angioplasty (PTCA) and lysis and can be used as anticoagulants in the extracorporeal circulation (heart-lung machine, hemodialysis). They can also be generally used for thrombosis prophylaxis, for example after surgical interventions.

It is known that synthetic arginine derivatives influence the enzyme activity of the thrombin by interacting with the active serine residue of the protease thrombin. Peptides based on Phe-Pro-Arg, in which the N-terminal amino acid is present in the D form, have proven particularly favorable. D-Phe-Pro-Arg isopropyl ester is described as a competitively acting thrombin inhibitor (C. Mattson et. al. Folia Haematol, 109, 43 to 51, 1983).

WO 94/29336, EP 0601459, WO 95/23609, EP 0672658, WO 97/23499, WO 98/06740 and WO 95/35309 represent a further development in which the agmatine residue is replaced by an arylamidine residue.

Although these compounds have significant antithrombotic action, it is advantageous to improve their pharmacokinetic properties after oral or parenteral administration.

Inter alia, the influencing of the following pharmacokinetic properties is desirable:

I. The improvement of the absorption from the gastrointestinal tract with the aim of a high bioavailability.

II. The minimization of the inter- and intraindividual variability of the bioavailability by means of constant absorption

III. The achievement of therapeutically relevant activity levels, which are as constant as possible, over the time course. With respect to the therapeutic breadth, plasma concentrations which are as constant as possible over the time course are indispensable, as variations which are too great can lead to undesired side effects. If the plasma concentration of the active compound is too high, bleeding can be expected; if the concentration is too low the risk of thrombus formation increases.

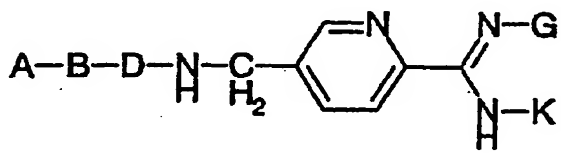
IV. The prolongation of the duration of action of the active compound: Active compound is understood as meaning the pharmacologically active substance (drug) in comparison to the substance (prodrug), which first has to be converted into the active compound metabolically.

V. Reduction of trypsin inhibition: since the prodrugs affect the digestive enzyme trypsin markedly less, fewer side effects are to be expected with the prodrugs.

A further advantage of the prodrugs compared with the drugs lies in the fact that high local concentrations of the drugs do not occur outside the target site. Moreover, with less selective drugs side effects are minimized, as, for example, in the gastrointestinal tract no further serine proteases are inhibited if the drug is essentially formed by metabolism of the prodrug only after or during gastrointestinal passage.

The aim of this invention is the improvement of the pharmacokinetic properties of the thrombin inhibitors mentioned in particular in WO 95/35309 and WO 96/25426 by means of suitable prodrugs.

The invention relates to compounds of the formula I



(I)

in which A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $HO-CH_2-CH_2-$, $R^2R^3N(O)C-CH_2-$, $R^2R^3N-O-CO-CH_2-$, $R^2N(OH)-CO-CH_2-$, where R^2 and R^3 independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_3-alkyl, or benzyl, or R^2 and R^3 together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ (q = 1-4), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where a phenyl ring can be fused to the cycloalkyl ring, pyranyl-, piperidinyl-, aryl- or phenyl-C_1-C_3-alkyl-, where except for H all radicals mentioned can optionally carry up to 4 identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals, or
R^1 is (2-oxo-1,3-dioxolen-4-yl)methyl-, which can be substituted in the 5-position by C_1-C_{16}-alkyl or aryl,

or

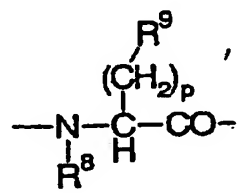
R^1 is: $R^4-C(O)O-C(R^5)_2-$, $R^4-C(O)NR^2-C(R^5)_2-$, where R^4 can be C_1-C_4-alkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, C_3-C_8-cycloalkyl-, C_1-C_4-alkyloxy-, C_3-C_8-cycloalkyl-C_1-C_3-alkyloxy-, C_3-C_8-cycloalkyloxy-, aryl- or phenyl-C_1-C_6-alkyl-, the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, and R^2 has the meaning indicated above,
$R^6OOC-C_1-C_6$-alkyl, $R^6R^7N(O)C-C_1-C_6$-alkyl-, $R^6R^7N-C_2-C_6$-alkyl-, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl, or

if R^1 is $R^6R^7N(O)C—C_1—C_6$—alkyl—, R^6 and R^7 together form a C_4-C_6-alkylene chain,

or A is:

C_1-C_4-alkyl-SO_2-$(CH_2)_{2-6}$- , HO_3S-$(CH_2)_{4-6}$-, 5-tetrazolyl-$(CH_2)_{1-6}$-, C_1-C_4-alkyl-O-$(CH_2)_{2-6}$-, R^2R^3N-$(CH_2)_{2-6}$-, R^2S-$(CH_2)_{2-6}$-, $R^2R^3NSO_2$-$(CH_2)_{2-6}$-, HO-$(CH_2)_{2-6}$-,

B is



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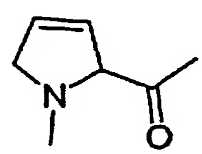
p is 0,1,2

R^8 is H—, $R^{10}OOC$- where R^{10}= C_{1-16}—alkyl—, phenyl—, C_3—C_8—cycloalkyl—, phenyl-C_1-C_4-alkyl-, $R^{11}C(O)$-O-CH_2-, $R^{11}C(O)$-O-$CH(CH_3)$-, where R^{11} can be C_1-C_4-alkyl-, phenyl-, benzyl-, C_3—C_8—cycloalkyl- or cyclohexyl-CH_2-,

R^9 is C_{3-8}—cycloalkyl—, which can carry up to four identical or different C_{1-4}—alkyl radicals,

D is:



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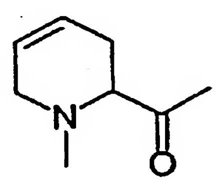


(III)

G is: -H, -OH, -OR^{12},

in which

R^{12} is: -C_{1-8}—alkyl, -C_3—C_8—cycloalkyl, -C_1-C_3-alkyl-C_3-C_8-cycloalkyl, -aryl or -C_1-C_6-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals,

K is: H,

or G and K together form a —C(O)O-group,

their configurational isomers, tautomers and their salts with physiologically tolerable acids,
where the following applies:

(i)

if D = (II) or (III) and G = -H, -OH, $-OR^{12}$,
in which
R^{12} is: $-C_1-C_8$-alkyl, $-C_1-C_3$-alkyl-C_3-C_8-cycloalkyl, -aryl or $-C_1-C_6$-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals

K is: H,
or G and K together form a -C(O)O-group, then A and B have the following meanings:
A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $HO-CH_2-CH_2-$, $R^{2a}R^{3a}N(O)C-CH_2-$, $R^2R^3N-O-CO-CH_2-$, $R^2N(OH)-CO-CH_2-$, where R^2 and R^3 independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl or R^2 and R^3 together form a C_4-C_6-alkylene chain, R^{2a} is equal to H and R^{3a} is C_5-C_8-alkyl, C_3-C_8-cycloalkyl or benzyl;

in which

R^1 is: C_5-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ (q = 1–4), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where the phenyl ring can be fused to the cycloalkyl ring, pyranyl-, piperidinyl-, or aryl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals, or
R^1 is 2-oxo-1,3-dioxolen-4-yl)methyl- which can be substituted in the 5-position by C_1-C_{16}-alkyl or aryl,

or

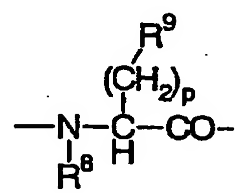
R^1 is: $R^4-C(O)O-C(R^5)_2-$, $R^4-C(O)NR^2-C(R^5)_2-$, where R^4 can be C_1-C_4-alkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, C_3-C_8-cycloalkyl-, C_1-C_4-alkyloxy-, C_3-C_8-cycloalkyl-C_1-C_3-alkyloxy-, C_3-C_8-cycloalkyloxy-, aryl- or phenyl-C_1-C_6-alkyl-, the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, and R^2 has the meaning indicated above,
$R^6OOC-C_1-C_6$-alkyl-, $R^6R^7N(O)C-C_1-C_6$-alkyl-, $R^6R^7N-C_2-C_6$-alkyl-, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl, or

if R^1 is $R^6R^7N(O)C-C_1-C_6$-alkyl-, R^6 and R^7 together form a C_4-C_6-alkylene chain,

or A is:

C_1-C_4-alkyl-$SO_2-(CH_2)_{2-6}$- , $HO_3S-(CH_2)_{4-6}$-, 5-tetrazolyl-$(CH_2)_{1-6}$-, C_1-C_4-alkyl-O-$(CH_2)_{2-6}$-, $R^2R^3N-(CH_2)_{2-6}$-, $R^2S-(CH_2)_{2-6}$-, $R^2R^3NSO_2-(CH_2)_{2-6}$-, $HO-(CH_2)_{2-6}$-,

B is



p is 0,1,2

R^8 is H-, $R^{10}OOC$- where R^{10}= C_{1-16}-alkyl-, phenyl-, C_3-C_8-cycloalkyl-, phenyl-C_1-C_4-alkyl-, $R^{11}C(O)-O-CH_2$-, $R^{11}C(O)-O-CH(CH_3)$-, where R^{11} can be C_1-C_4-alkyl-, phenyl-, benzyl-, C_3-C_8-cycloalkyl- or cyclohexyl-CH_2-,

R^9 is C_{3-8}-cycloalkyl-, which can carry up to four identical or different C_{1-4}-alkyl radicals,

ia)

Preferred compounds of the formula I in i) are those in which A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2$-, $R^1OOC-CH_2-CH_2$-, $R^1OOC-CH(CH_3)$-,

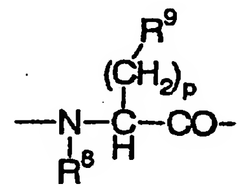
in which

R^1 is: C_5-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ (q = 1–4), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where a phenyl ring can be fused to the cycloalkyl ring, pyranyl- piperidinyl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3, CF_3, F, Cl, HO or methoxy radicals, or
R^1 is (2-oxo-1,3-dioxolen-4-yl)methyl-, which can be substituted in the 5-position by C_1-C_3-alkyl or aryl,

or

R^1 is: R^4—C(O)O—C(R^5)$_2$—, where R^4 C_1—C_4—alkyl—, C_3—C_8—cycloalkyl—, C_1—C_4—alkyloxy—, C_3—C_8—cycloalkyl—C_1—C_3—alkyloxy—, C_3—C_8—cycloalkyloxy—, or aryl— the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, R^6OOC—C_1—C_6—alkyl—, R^6R^7N(O)C—C_1—C_6—alkyl—, R^6R^7N—C_2—C_6—alkyl—, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl or, if R^1 is R^6R^7N(O)C—C_1—C_6—alkyl—, R^6 and R^7 together form a C_4-C_6-alkylene chain,

B is



p is 0,1

R^8 is H—, R^{10}OOC- and R^{10}= C_{1-8}—alkyl—, phenyl—, C_3—C_8—cycloalkyl—, phenyl-C_1-C_4-alkyl-,
R^9 is C_{3-8}—cycloalkyl—, which can carry up to four identical or different C_{1-4}—alkyl radicals,

D = (II)

and G = -H, -OH, -O-C_1—C_8—alkyl,
K is: H
or G and K together form a —C(O)O-group.

(ii)

if D = (II) or (III) and G = -OR^{12},
in which
R^{12} is: -C_5—C_8—alkyl, -C_3-C_8-cycloalkyl, -C_1-C_3-alkyl-C_3-C_8-cycloalkyl, -aryl or -C_1-C_6-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals,

K is: H,
or G and K together form a —C(O)O-group, then A and B have the following meanings:

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^{2a}R^{3a}N(O)C-CH_2-$, where R^{2a} and R^{3a} independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl or R^{2a} and R^{3a} together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_4-alkyl- or phenyl-C_1-C_4-alkyl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals,

B, p and R^8, R^9, R^{10} and R^{11} have the meaning indicated in i).

iia)

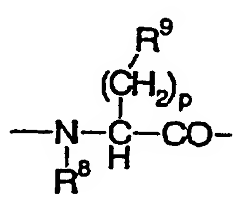
Preferred compounds of the formula I in ii) are those in which A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^{2a}R^{3a}N(O)C-CH_2-$, where R^{2a} and R^{3a} independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl, or R^{2a} and R^{3a} together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_4-alkyl- or phenyl-C_1-C_4-alkyl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3, CF_3, F, Cl, HO or methoxy radicals,

B is



p is 0,1

R^8 is H-, $R^{10}OOC-$ and R^{10}= C_{1-16}-alkyl-, phenyl-, C_3-C_8-cycloalkyl-, benzyl-,

and R^9 has the meaning indicated in i)
D = (II)
G = $-OR^{12}$,

in which

R^{12} is: $-C_5-C_8$-alkyl, $-C_3-C_8$-cycloalkyl, $-C_1-C_3$-alkyl-C_3-C_8-cycloalkyl, -aryl or $-C_1-C_6$-alkylphenyl, which can optionally carry up to three CH_3-, CF_3-, F-, Cl-, or methoxy radicals,

K is: H,

or G and K together form a -C(O)O-group.

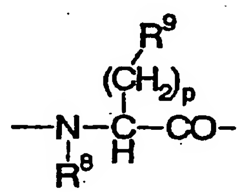
Particularly preferred prodrugs of the formula I are those where A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$,

in which

R^1 is: C_5-C_{10}-alkyl-, C_4-C_7-cycloalkyl-, C_4-C_7-cycloalkyl-CH_2-, where all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3- and methoxy-,

B is

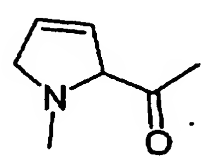


p is 0,1,

R^8 is H-,

R^9 is C_{4-7}-cycloalkyl-, which can carry up to four identical or different methyl or ethyl radicals

D is:



(II)

G is: -OH,

K is: H.

The aforementioned compounds belong to three groups of substances:

- The first group comprises prodrugs of thrombin inhibitors (e.g. G equals -OH, $-OR^{12}$) which is a substance to only a negligible antithromotic effect, which, however, are converted in the organism into the active substance (G equals H). These compounds are included in all claims. The advantage of the prodrugs lies in their improved pharmacokinetic and pharmacodynamic behaviour in the organism. Compounds wherein G equals -OH, $-OR^{12}$, and simultaneously A equals $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$ etc. are double prodrugs which are converted in the organism into the respective drug (G equals -H, A equals $HOOC-CH_2-$ etc.) by converting both prodrug groups.

- The second group comprises prodrugs of thrombin inhibitors which show already as a prodrug a thrombin-inhibiting effect (e.g. A equals $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$ etc. in combination with G equals -H). The effective substance formed in the organism (drug; A equals $HOOC-CH_2-$, $HOOC-CH_2-CH_2-$, $HOOC-CH(CH_3)-$ etc., G equals -H) shows also a thrombin-inhibiting effect. These are in part compounds of claims 1 (i), 2 and 5. The advantage of these prodrugs lies also in their improved pharmacokinetic and pharmacodynamic behaviour in the organism.

- The third group comprises thromin inhibitors which per se show the antithrombotic effect (e.g. A equals C_{1-4}-alkyl-$SO_2-(CH_2)_{2-6}-$, $HO_3-S-(CH_2)_{2-6}-$, 5-tetrazolyl-$(CH_2)_{1-6}-$, C_{1-4}-alkyl-$O-(CH_2)_{2-6}-$, $R^2R^3N-(CH_2)_{2-6}-$, $R^2S-(CH_2)_{2-6}-$, $R^2R^3NSO_2-(CH_2)_{2-6}-$, in combination with G equals -H). Such compounds are included in claim 1 (i).

The following compounds, their configurational isomers, tautomers, and salts with physiologically tolerable acids are furthermore the subject of this invention:

HOOC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
H_3CO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
EtO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
nPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
nBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
iBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
tBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
BnO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
HOOC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
EtO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
nPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
iPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
nBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
iBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
tBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
H_3CO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
EtO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
nPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
nBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
iBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
tBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico
H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
EtO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
nPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
nBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
iBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
tBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico
HOOC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(O-Allyl)]-pico
H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OCH_3)]-pico
iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OCH_3)]-pico

The following substances are particularly preferred:

1.	CH_3-$(CH_2)_{15}$O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
2.	CH_3-$(CH_2)_{10}$O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
3.	Piperidin-1-yl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
4.	Piperidin-4-yl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
5.	Decalinyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
6.	^{t}Bu-cHexyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
7.	Ada-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
8.	4-^{t}Bu-cHexyl-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
9.	^{c}Hept-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
10.	3,3,5,5-TetraMe-cHex-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
11.	4-Pyranyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
12.	2,4-DiMe-3-Pentyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
13.	1-Me-cPentyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
14.	a,a-Di-cHex-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
15.	^{t}Bu-N-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
16.	nHex-N-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
17.	HO-NH-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
18.	cPent-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
19.	cHex-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
20.	cHex-N(OH)-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
21.	iPr-N(OH)-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
22.	CH_3-N(OH)-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
23.	H_2N-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
24.	c$(CH_2)_5$N-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
25.	N-Me-4-Pip-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
26.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
27.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
28.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
29.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
30.	Cyclopropylmethyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
31.	1,3-Dioxol-2-on-4-enyl-O-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
32.	Cyclopropylmethyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
33.	1,3-Dioxol-2-on-4-enyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
34.	Cyclopropylmethyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
35.	1,3-Dioxol-2-on-4-enyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
36.	Cyclopropylmethyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
37.	1,3-Dioxol-2-on-4-enyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
38.	CH_3-$(CH_2)_{15}$O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
39.	CH_3-$(CH_2)_{10}$O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
40.	Piperidin-1-yl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
41.	Piperidin-4-yl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
42.	Decalinyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico

43.	tBu-cHexyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
44.	Ada-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
45.	4-^{t}Bu-cHexyl-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
46.	cHept-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
47.	3,3,5,5-TetraMe-cHex-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
48.	4-Pyranyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
49.	2,4-DiMe-3-Pentyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
50.	1-Me-cPentyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
51.	a,a-Di-cHex-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
52.	tBu-N-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
53.	nHex-N-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
54.	HO-NH-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
55.	cPent-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
56.	cHex-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
57.	cHex-N(OH)-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
58.	iPr-N(OH)-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
59.	CH_3-N(OH)-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
60.	H_2N-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
61.	c$(CH_2)_5$N-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
62.	N-Me-4-Pip-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
63.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
64.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
65.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
66.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
67.	nOctO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
68.	cHex-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
69.	neoPentO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
70.	CH_3-O$(CH_2)_2$O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
71.	CH_3-$[O(CH_2)_2]_2$O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
72.	cHex-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
73.	cOctO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
74.	4-Me-cHexyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
75.	nHexO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
76.	cPentO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
77.	4-MeO-cHexyl-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
78.	2,3-DiMe-2-Bu-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
79.	2-Me-1,3-Dioxane-5-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
80.	2,4-DiMe-3-Pent-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
81.	2-Indan-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
82.	2,6-DiMe-4-Hept-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
83.	Pyrr-N-CO-$(CH_2)_3$-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
84.	cHex-N-CO-CH_2-O-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
85.	CH_3-$(CH_2)_{15}$O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
86.	CH_3-$(CH_2)_{10}$O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
87.	Piperidin-1-yl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
88.	Piperidin-4-yl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
89.	Decalinyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
90.	tBu-cHexyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
91.	Ada-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico

92.	4-^{t}Bu-cHexyl-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
93.	cHept-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
94.	3,3,5,5-TetraMe-cHex-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
95.	4-Pyranyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
96.	2,4-DiMe-3-Pentyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
97.	1-Me-cPentyl-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
98.	a,a-Di-cHex-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
99.	tBu-N-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
100.	nHex-N-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
101.	HO-NH-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
102.	cPent-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
103.	cHex-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
104.	cHex-N(OH)-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
105.	iPr-N(OH)-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
106.	CH_3-N(OH)-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
107.	H_2N-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
108.	c(CH_2)$_5$N-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
109.	N-Me-4-Pip-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
110.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
111.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
112.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
113.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
114.	CH_3-$(CH_2)_{15}$O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
115.	CH_3-$(CH_2)_{10}$O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
116.	Piperidin-1-yl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
117.	Piperidin-4-yl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
118.	Decalinyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
119.	tBu-cHexyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
120.	Ada-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
121.	4-^{t}Bu-cHexyl-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
122.	cHept-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
123.	3,3,5,5-TetraMe-cHex-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
124.	4-Pyranyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
125.	2,4-DiMe-3-Pentyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
126.	1-Me-cPentyl-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
127.	a,a-Di-cHex-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
128.	tBu-N-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
129.	nHex-N-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
130.	HO-NH-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
131.	cPent-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
132.	cHex-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
133.	cHex-N(OH)-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
134.	iPr-N(OH)-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
135.	CH_3-N(OH)-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
136.	H_2N-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
137.	c(CH_2)$_5$N-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
138.	N-Me-4-Pip-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
139.	$(CH_3)_3C$-CO_2-CH_2-O-OC-CH_2-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico

140.	(CH$_3$)$_3$C-CO$_2$-CH$_2$-O-OC-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
141.	(CH$_3$)$_3$C-CO$_2$-CH$_2$-O-OC-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
142.	(CH$_3$)$_3$C-CO$_2$-CH$_2$-O-OC-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
143.	cHN$_4$C-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
144.	cHN$_4$C-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
145.	NH$_2$-CH$_2$-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
146.	NH$_2$-CH$_2$-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
147.	NH$_2$-CH$_2$-CH$_2$-(D)-Chg-Dep-NH-3-[6-am-(OH)]-pico
148.	(CH$_3$)$_2$N-CH$_2$-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
149.	(CH$_3$)$_2$N-CH$_2$-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
150.	(CH$_3$)$_2$N-CH$_2$-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
151.	CH$_3$-NH-SO$_2$-CH$_2$-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
152.	CH$_3$-NH-SO$_2$-CH$_2$-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
153.	CH$_3$-NH-SO$_2$-CH$_2$-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
154.	H$_2$N-SO$_2$-CH$_2$-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico
155.	H$_2$N-SO$_2$-CH$_2$-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico
156.	H$_2$N-SO$_2$-CH$_2$-CH$_2$-(D)-Cha-Dep-NH-3-[6-am-(OH)]-pico
157.	HO-OC-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(-COO-)]-pico
158.	MeO-OC-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(-COO-)]-pico
159.	HO-OC-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(-COO-)]-pico
160.	MeO-OC-CH$_2$-(D)-Chg-Pyr-NH-3-[6-am-(-COO-)]-pico
161.	EtO-OC-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(-COO-)]-pico
162.	cHexO-OC-CH$_2$-(D)-Cha-Pyr-NH-3-[6-am-(-COO-)]-pico

List of abbreviations:

Adaala:	Adamantylalanine
Adagly:	Adamantylglycine
AIBN:	Azobisisobutyronitrile
Ac:	Acetyl
Ala:	Alanine
am:	Amidino
Asp:	Aspartic acid
Aze:	Azetidinecarboxylic acid
Bn:	Benzyl
Boc:	tert-Butyloxycarbonyl
Bu:	Butyl
Cbz:	Benzyloxycarbonyl
Cha:	Cyclohexylalanine
Chea:	Cycloheptylalanine
Cheg:	Cycloheptylglycine
Chg:	Cyclohexylglycine
Cog:	Cyclooctylglycine
Cpa:	Cyclopentylalanine
Cpg:	Cyclopentylglycine
DC:	Thin-layer chromatography
DCC:	Dicyclohexylcarbodiimide
Dch:	Dicyclohexylalanine

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Dcha:	Dicyclohexylamine
DCM:	Dichlormethane
Dep:	4,5-Dehydropipecolic acid
DMF:	Dimethylformamide
DIPEA:	Diisopropylethylamine
Et:	Ethyl
Eq:	Equivalent
Gly:	Glycine
ham:	Hydroxyamidino
HOSucc:	Hydroxysuccinimide
HPLC:	High-performance liquid chromatography
iPr:	Isopropyl
Lsg:	Solution
Me:	Methyl
bb-Me_2Cha:	2-Amino-3-cyclohexyl-3-methylbutyric acid or bb-Dimethylcyclohexylalanine
4-MeCha:	(4-Methylcyclohex-1-yl)alanine
g-MeCha:	(1-Methylcyclohex-1-yl)alanine
3,3-Me_2Cha:	(3,3-Dimethylcyclohex-1-yl)alanine
4-MeChg:	(4-Methylcyclohex-1-yl)glycine
3,3-Me_2Chg:	(3,3-Dimethylcyclohex-1-yl)glycine
MPLC:	Medium-pressure liquid chromatography
MTBE:	Methyl-tert-butyl ether
NBS:	N-Bromsuccinimide
Nog:	Norbornylglycine
Oxaz:	Oxazole
Ph:	Phenyl
phe:	Phenylalanine
Pic:	Pipecolic acid
pico:	Picolyl
PPA:	Propylphosphonic anhydride
pro:	Proline
Py:	Pyridine
Pyr:	3,4-Dehydroproline
pyraz:	Pyrazole
pyrr:	Pyrrole
RT:	Room temperature
RP-18	Reversed phase C-18
t:	Tertiary
tBu:	tertiary-Butyl
tert:	Tertiary
TBAB:	Tetrabutylammonium bromide
TEA:	Triethylamine
TFA:	Trifluoroacetic acid
TFAA:	Trifluoroacetic anhydride
thiaz:	Thiazole

thioph:	Thiophene
TOTU:	O–(Cyanoethoxycarbonylmethylene)amino–]–N,N,N′,N′–tetramethyluronium tetrafluoroborate
Z:	Benzyloxycarbonyl
nPent:	n–Pentyl
neoPent:	neo–Pentyl (2,2–dimethyl–1–propyl)
nHex:	n–Hexyl
cHex:	Cyclohexyl
c–Pent	Cyclopentyl
cHN_4C–	Tetrazolyl– (3–tetrazolyl– or 5–tetrazolyl)
$c(CH_2)_5N$–	N–Piperidinyl
nOct:	n–Octyl
O–p–Me–Bn:	p–Methylbenzyloxy–
N–Me–4–Pip–OH	N–Methyl–4–piperidinyl alcohol
MeO–tetraethoxy:	Tetraethylene glycolyl monomethyl ether
$CH_3-(CH_2)_{15}O$:	Hexadecyloxy
$CH_3-(CH_2)_{10}O$:	Undecyloxy
4–Pip–O:	4–Piperidinyloxy
1–Pip–O:	1–Piperidinyloxy
tBu–cHexyl–O:	4–tert–Butyl–cyclohexyloxy
Ada–CH_2–O:	1–Adamanthylmethyloxy
4–^{t}Bu–cHexyl–CH_2–O:	4–tert–Butylcyclohexylmethyloxy
cHept–O:	Cycloheptyloxy
3,3,5,5–tetraMe–cHex–O:	3,3,5,5–Tetramethylcyclohexanyloxy
4–Pyranyl–O:	4–Pyranyloxy
nPrO:	n–Propyloxy
nBu–O:	n–Butyloxy
iBu–O:	t–Butyloxy
2,4–diMe–3–Pentyl–O:	1–Isopropyl–2–methylpropyloxy
1–Me–cPentyl–O:	1–Methyl–cyclopentyloxy
a,a–di– cHex–CH_2–O:	Dicyclohexylmethoxy
tBu–N:	tert–Butylamino
nHex–N:	n–Hexylamino
H_2N-3-[6-am-(-COO-)]-pico:	3-[5-(aminomethyl)-2-pyridinyl]-1,2,4-oxadiazol-5-one
H_2N-3-[6-am-(OH)]-pico:	5-(aminomethyl)-N'-hydroxy-2-pyridin-carboximidamide

In the description and the claims, the following definitions apply to the individual substituents:

The term "cycloalkyl" per se or as part of another substituent includes saturated, cyclic hydrocarbon groups which contain the number of carbon atoms indicated and in which up to two CH_2 groups can be replaced by oxygen, sulfur or nitrogen atoms. C_{3-8}-cycloalkyl relates to saturated alicyclic rings having 3 to 8 C atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, cyclohexylmethylene, cycloheptyl or cyclooctyl, pyrrolidine, piperidine, morpholine. Pure carbocycles are preferred.

The term "alkyl" per se or as part of another substituent denotes a linear or branched alkyl chain radical of the length indicated in each case, which can be saturated or unsaturated and in which up to 5 CH_2 groups can be replaced by oxygen, sulfur or nitrogen atoms. In this case, the heteroatoms are separated from one another by at least two carbon atoms. Thus C_{1-4}-alkyl is, for example, methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 1-but-2-enyl, 2-butyl, C_{1-6}-alkyl, for example, C_{1-4}-alkyl, pentyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl or 3,3-dimethylbutyl. C_{1-8}-alkyl is additionally the radicals indicated for C_{1-4}-alkyl, e.g. C_{1-6}-alkyl, heptyl, 2-(2-methoxyethoxy)ethyl or octyl. The saturated alkyl chains without heteroatoms are preferred.

The term "alkoxy" per se or as part of another substituent denotes a linear or branched alkyl chain radical of the length indicated in each case, which can be saturated or unsaturated and is bonded to the respective parent compound via an oxygen atom. Thus C_{1-4}-alkoxy is, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy, 2-methyl-2-propoxy, 2-methyl-1-propoxy, 1-butoxy, 2-butoxy.

The term "aryl" per se or as part of another substituent includes mono-, bi- or tricyclic aromatic hydrocarbons, such as phenyl. naphthyl, tetralinyl, indenyl, fluorenyl, indanyl, anthracenyl, phenanthrenyl.

The compounds of the formula I can be present as such or in the form of their salts with physiological tolerable acids. Examples of acids of this type are: hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric aid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric

acid, aspartic acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

The novel compounds of the formula I can be employed in the following indications:

- disorders whose pathological mechanism is based directly or indirectly on the proteolytic action of thrombin,
- disorders whose pathological mechanism is based on the thrombin-dependent activation of receptors and signal transduction,
- disorders which are accompanied by stimulation [e.g. by PAI-1, PDGF (platelet-derived growth factor, P-Selectin, ICAM-1, Tissue factor] or inhibition (e.g. NO synthesis in smooth muscle cells) of gene expression in body cells,
- disorders which are based on the mitogenic action of thrombin,
- disorders which are based on a thrombin-dependent contractility and permeability change in epithelial cells (e.g. vascular endothelial cells),
- thrombin-dependent, thromboembolic events such as deep vein thrombosis, pulmonary embolism, myocardial or cerebral infarct, atrial fibrillation, bypass occlusion,
- disseminated intravasal coagulation (DIC),
- reocclusion and for the reduction of the reperfusion time in the case of comedication with thrombolytics such as streptokinase, urokinase, prourokinase, T-PA, APSAC, plasminogen activators from the salivary glands of animals, and the recombinant and mutated forms of all these substances,
- the occurrence of earlier reocclusion and later restenosis after PTCA,
- the thrombin-dependent proliferation of smooth muscle cells,
- the accumulation of active thrombin in the CNS (e.g. in Alzheimer's disease),

- tumor growth and against the adhesion and metastasis of tumor cells.

In particular, the novel compounds can be employed for the therapy and prophylaxis of thrombin-dependent thromboembolic events such as deep vein thromboses, pulmonary embolisms, myocardial or cerebral infarcts and unstable angina, and furthermore for the therapy of disseminated intravasal coagulation (DIC). They are furthermore suitable for combination therapy with thrombolytics such as streptokinase, urokinase, prourokinase, t-PA, APSAC and other plasminogen activators for reduction of the reperfusion time and prolongation of the reocclusion time.

Further preferred application areas are the prevention of thrombin-dependent early reocclusion and late restenosis after percutaneous transluminal coronary angioplasty, the prevention of thrombin-induced proliferation of smooth muscle cells, the prevention of the accumulation of active thrombin in the CNS (e.g. in Alzheimer's disease), tumor control and the prevention of mechanisms which lead to adhesion and metastasis of tumor cells.

The novel compounds can further be employed in disorders whose pathological mechanism is based directly or indirectly on the proteolytic action of kininogenases, in particular kallikrein, e.g. in inflammatory conditions such as asthma, pancreatitis, rhinitis, arthritis, urticaria and other internal inflammatory conditions.

The compounds according to the invention can be orally administered in the customary manner. Administration can also be carried out through the nasopharyngeal space using vapors or sprays.

The dose depends on the age, condition and weight of the patient and on the manner of administration. As a rule, the daily dose of active compound per person is between approximately 10 and 2000 mg in the case of oral administration. This dose can be given in 2 to 4 individual doses or once daily as a slow-release form.

The novel compounds can be administered in solid or liquid form in the customary pharmaceutical administration forms, e.g. as tablets, film-coated tablets, capsules, powders, granules, coated tablets, solutions or sprays. These are prepared in the customary manner. The active compounds can in this case be processed with

the customary pharmaceutical excipients such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-delaying agents, antioxidants and/or propellants (cf. H. Sucker et al.: Pharmazeutische Technologie [Pharmaceutical Technology], Thieme-Verlag, Stuttgart, 1978). The administration forms thus obtained normally contain the active compound in an amount from 0.1 to 99% by weight.

Experimental section

Pharmacological tests

The absorption rate of orally administered medicaments from the gastrointestinal tract (GIT) is an important factor with respect to the bioavailability of the medicament. A prerequisite for a high bioavailability is a good absorption rate.

A number of in vitro models are available for the study of intestinal absorption. Thus, the human colon adenocarcinoma cell lines THE-29, Caco-2 and T84 are routinely employed in order to investigate various intestinal transport processes (Madara et al., *Am. J. Physiol*. 1988, *254*: G416-G423; K. L. Audus et al, *Pharm. Res*. 1990, *7*, 435-451). The IEC-18 cell line also proved to be a suitable model for the investigation of the permeability of hydrophibic substances through the intestinal membrane (Ma et al., *J. Lab. Clin. Med*. 1992; Duizer et al., *J. Contr. Rel*. 1997).

For the transport experiments (Materials, Methods: see R.T. Borchardt, P.L. Smith, G. Wilson, *Models for Assessing Drug Absorption and Metabolism*, 1st Edition, Plenum Press New York and London, 1996, Chapter 2), the cells are cultured for 17-24 days on Transwell polycarbonate membranes. The experimental chamber is arranged such that the membrane separates the apical compartment from the basolateral compartment. The transport of the test substances from the apical side through the cell layer to the basolateral side can be measured as a function of the pH gradient, e.g. apical (pH 6.0) basolateral (pH 8.0).

After incubation of the cells with the test substance, samples are removed from the apical and basolateral sides after a defined time interval (e.g. 24 h). The content of test substance employed and possible metabolites in each of the two compartments is determined by HPLC (comparison of retention times) and HPLC-MS

(elucidation of metabolites) analysis. The transport rate is calculated.

With the aid of the values which these tests produce, it is possible to divide the test substances into the following categories:

+++ : very good transport
++ : good transport
+ : moderate transport
o : poor transport

In the table below, the division into the categories mentioned has been carried out for selected examples:

Ex. No.	Transport
01	++
03	++
05	+++
07	+
14	+++
15	+++
31	o
32	+

Pharmacokinetics and clotting parameters in rats

The test substances are dissolved in isotonic saline solution immediately before administration to conscious Sprague Dawley rats. The administration volumes are 1 ml/kg for intravenous bolus injection into the tail vein and 10 ml/kg for oral administration, which is carried out by stomach tube. If not mentioned otherwise, taking of blood is carried out 1 h after oral administration of 21.5 $mg \cdot kg^{-1}$ or intravenous administration of 1.0 $mg \cdot kg^{-1}$ of the test substance or of the corresponding vehicle (control). Five minutes before taking blood, the animals are anesthetized by i.p. administration of 25% strength urethane solution (dose 1 $g \cdot kg^{-1}$ i.p.) in physiological saline solution. The carotid artery is dissected and catheterized and blood samples (2 ml) are taken in citrate tubes (1.5 parts of citrate plus 8.5 parts of blood). Directly after taking samples, the ecarin clotting time (ECT) in whole blood is determined. After the preparation of the plasma by centrifugation, the plasma

thrombin time and the activated partial thromboplastin time (APTT) are determined with the aid of a coagulometer.

Clotting parameters:

Ecarin clotting time (ECT): 100 µl of citrated blood are incubated for 2 min at 37°C in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG). After the addition of 100 µl of prewarmed (37°C) ecarin reagent (Pentapharm), the time until formation of a fibrin clot is determined.

Activated thromboplastin time (APTT): 50 µl of citrate plasma and 50 µl of the PTT reagent (Pathrombin, Behring) are mixed and incubated for 2 min at 37°C in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG). After the addition of 50 µl of prewarmed (37°C) calcium chloride, the time until formation of a fibrin clot is determined.

Thrombin time (TT): 100 µl of citrate-treated plasma are incubated for 2 min at 37°C in a coagulometer (CL-8, ball type, Bender & Hobein, Munich, FRG). After the addition of 100 µl of prewarmed (37°C) thrombin reagent (Boehringer Mannheim), the time until the formation of a fibrin clot is determined.

Pharmacokinetics and clotting parameters in dogs

The test substances are dissolved in isotonic saline solution immediately before administration to conscious mongrel dogs. The administration volumes are 0.1 ml/kg for intravenous bolus injection and 1 ml/kg for oral administration, which is carried out by stomach tube. Before and 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min (if required after 420, 480 min and 24 h) after intravenous administration of 1.0 mg/kg or before and 10, 20, 30, 60, 120, 180, 240, 300, 360, 480 min and 24 h after oral administration of 4.64 mg/kg, samples of venous blood (2 ml) are taken in citrate tubes. Directly after taking the samples, the ecarin clotting time (ECT) in the whole blood is determined. After the preparation of the plasma by centrifugation, the plasma thrombin time and the activated partial thromboplastin time (APTT) are determined with the aid of a coagulometer.
The anti-F IIa activity (ATU/ml) and the concentration of the substance are additionally determined by its anti-F-IIa activity in the plasma by means of chromogenic (S-2238) thrombin assay, calibration curves with r-hirudin and the test substance being employed.

The plasma concentration of the test substance is the basis for the calculation of the pharmacokinetic parameters: time of maximum plasma concentration (T max), maximum plasma concentration; plasma half-life, $t_{0.5}$; area under the curve (AUC); absorbed part of the test substance (F).

Clotting parameter:
Ecarin clotting time (ECT): 100 µl of citrate-treated blood are incubated for 2 min at 37°C in a coagulometer (CL 8, ball-type, Bender & Hobein, Munich, FRG). After the addition of 100 µl of prewarmed (37°C) ecarin reagent (Pentapharm), the time until the formation of a fibrin clot is determined.

Activated thromboplastin time (APTT): 50 µl of citrate-treated plasma and 0 µl of the PTT reagent (Pathrombin, Behring) are mixed and incubated for 2 min at 37°C in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG). After the addition of 50 µl of prewarmed (37°C) calcium chloride, the time until the formation of a fibrin clot is determined.

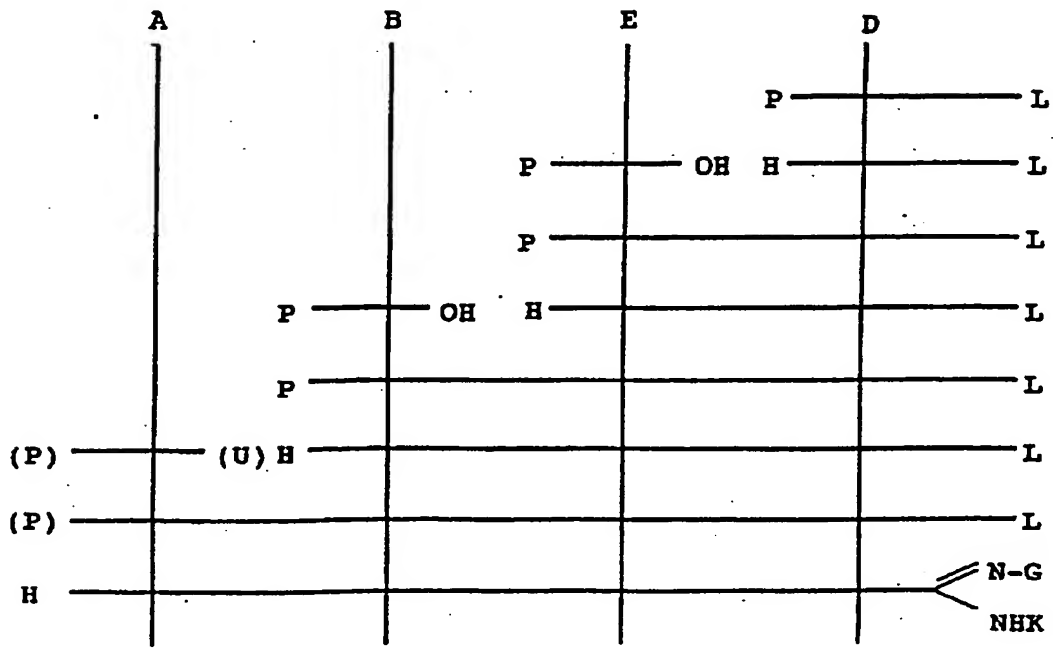
Thrombin time (TT): 100 µl of citrate-treated plasma are incubated for 2 min at 37°C in a coagulometer ((CL 8, ball type, Bender & Hobein, Munich, FRG). After the addition of 100 µl of prewarmed (37°C) thrombin reagent (Boehringer Mannheim), the time until the formation of a fibrin clot is determined.

As the prodrugs in some cases are very poor thrombin inhibitors, the proportion of active compound (drug) formed is determined directly by means of the determination of the clotting parameters. The kinetics therefore include the absorption of the prodrug, its metabolization and excretion, and the conversion into the active compound and its metabolization and excretion.

The compounds of the formula I can be prepared according to Schemes I-III.

The units A, B and D are preferably synthesized separately and employed in suitably protected form (see schemes I-III, use in each case of orthogonal protective groups (P or P*) compatible with the synthesis method used.

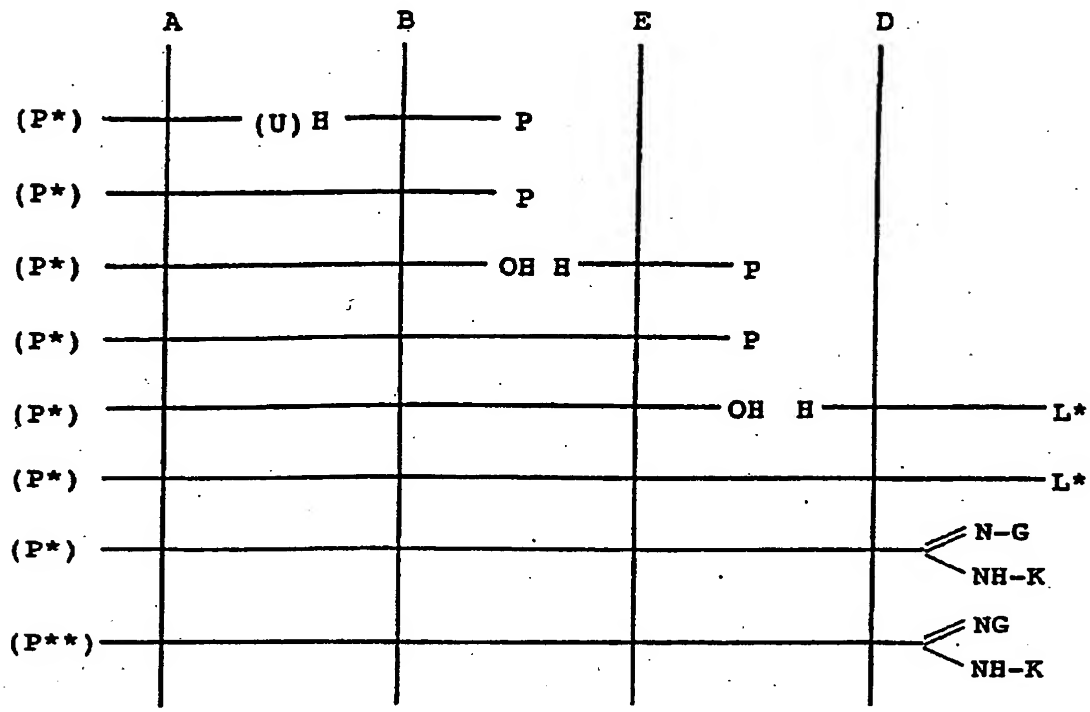
Scheme I



(P = protective group, (P) = protective group or H)

Scheme I describes the linear synthesis of the molecule I by protective group removal from P—D—L (L is equal to $CONH_2$, $CSNH_2$, CN), coupling of the amine H—D—L with the N-protected amino acid P—E—OH to give P—E—D—L, removal of the N-terminal protective groups to give H—E—D—L, coupling with the N-protected amino acid P—B—OH to give P—B—E—D—L, removal of the protective group P to give H—B—E—D—L, subsequent coupling or alkylation with the optionally protected (P)—A—U unit (U = leaving group) or reductive alkylation with (P)—A'—U (U = aldehyde, ketone) or Michael addition with a suitable P—A"—C=C— derivative to give (P)-A-B-E-D-L. If L is an amide function, this can be converted into the corresponding nitrile function at the in each case protected stages by dehydration using trifluoroacetic anhydride. Amidine syntheses of compounds of the structural type I starting from the corresponding carboximides, nitriles, thiocarboxamides and hydroxyamidines are described in a number of patent applications (see, for example WO 95/35309, WO 96/17860, WO 96/24609, WO 96/25426, WO 98/09950). Protective groups which may still be present are then removed.

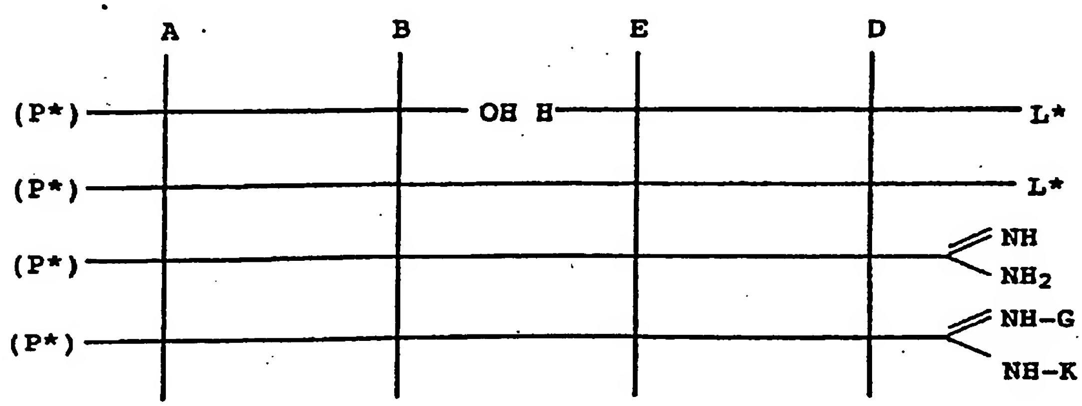
Scheme II



Scheme II describes the linear synthesis of the molecule I by coupling, alkylation, reductive amination or Michael addition of H–B–P to correspondingly suitable optionally protected (P*)–A units [(P*)–A–U (U = leaving group) or (P*)–A'–U (U = aldehyde, ketone), or (P*)–A″–C=C–derivative] to give (P*)-A-B–P. After removal of the C-terminal protective group to give (P*)-A-B–OH, coupling with H–E–P to give (P*)-A-B-E-P, removal of the C-terminal protective group again to give (P*)-A-B–E-OH and coupling with H–D–L* (L* is equal to $CONH_2$, $CSNH_2$, CN, C(=NH)NH-R*; R* is equal to a hydrogen atom or protective group) to give (P*)-A-B–E-D-L*, the reaction of this intermediate to give the final product is carried out analogously to Scheme I. The synthesis of the hydroxyl-, alkoxy- or aryloxyamidines (G = OH, OR) is carried out by reaction of the corresponding nitriles or iminothioester salts with hydroxylamine hydrochloride or O-substituted hydroxylamine derivatives. (P**) is then introduced by transesterification or starting from the free acid. For the synthesis of the oxadiazolones (G and K together form a COO-group), in particular of the three-substituted 1,2,4-oxadiazol-5-ones, the corresponding amidoximes are reacted, with addition of bases (e.g. NaOH, pyridine, tertiary amines), with carbonic acid derivatives such as, for example, phosgene, di- and triphosgene, carbonyldiimidazole or chloroformic acid

esters (R.E. Bolton et al., Tetrahedron Lett. 1995, 36, 4471; K. Rehse, F. Brehme, Arch. Pharm. Med. Chem. 1998, 331, 375).

Scheme III



Scheme III describes a very efficient route for the preparation of the compounds I by a convergent synthesis. The appropriately protected units (P*)—A—B-OH and H—E—D—L* are coupled to one another and the resulting intermediates (P*)—A—B-E—D—L* are reacted to give the final product analogously to scheme I and scheme II.

N—terminal protective groups employed are Boc, Cbz or Fmoc; C-terminal protective groups are methyl, tert-butyl and benzyl esters. Amidine protective groups are preferably Boc and Cbz. If the intermediates contain olefinic double bonds, protective groups which are removed hydrogenolytically are unsuitable.

The required coupling reactions and the customary reactions of protective group introduction and removal are carried out according to standard conditions of peptide chemistry (see M. Bodanszky, A. Bodanszky "The Practice of Peptide Synthesis", 2nd Edition, Springer Verlag Heidelberg, 1994).

Boc protective groups are removed by means of dioxane/HCl, diethyl ether/HCl, dichloromethane/HCl or TFA/DCM, Cbz protective groups hydrogenolytically or using HF, and Fmoc protective groups using piperidine. Ester functions are hydrolyzed using LiOH in an alcoholic solvent or in dioxane/water. t-Butyl esters are cleaved using TFA or dioxane/HCl.

The reactions were checked by means of TLC, the following eluents customarily being used:

A.	DCM/MeOH	95:5
B.	DCM/MeOH	9:1
C.	DCM/MeOH	8:2
D.	DCM/MeOH/50% strength HOAc	40:10:5
E.	DCM/MeOH/50% strength HOAc	35:15:5
F.	cyclohexane/EA	1:1

If column-chromatographic separations are mentioned, these separations were carried out on silica gel, for which the abovementioned eluents were used.

Reversed phase HPLC separations were carried out using acetonitrile/water and HOAc buffer.

The starting compounds can be prepared according to the following methods:

Units A prepared for alkylation are, for example, tert-butyl α-bromoacetate, adamantyl α-bromoacetate, tert-butyl β-bromopropionate, tert-butyl α-bromopropionate, tert-butyl α-bromobutyrate, 2,3-dimethyl-2-butyl α-bromoacetate, THP-protected bromoethanol, N-tert-butyl-α-bromoacetamide and N,N,-diethyl-α-bromoacetamide. The tert-butyl esters mentioned, if they cannot be purchased commercially, are prepared analogously to G. Uray, W. Lindner, Tetrahedron 1988, 44, 4357-4362. The bromoacetic acid esters, if they are not obtainable commercially, were prepared by reaction of bromoacetyl bromide with the appropriate alcohols with addition of pyridine as a base.

B units:

A variety of possibilities are available in the literature for the general and specific synthesis of amino acids. Volume E16d/Part 1 - H Houben-Weyl, pp. 406 et seq., inter alia, gives a general overview of this.

Frequently employed starting materials were ethyl benzophenoneiminoacetate, diethyl acetamidomalonate and ethyl isonitriloacetate.

The preparation of various glycine and alanine derivatives was carried out, for example, starting from ethyl isonitroloacetate and an appropriate ketone or aldehyde (see (H.J. Prätorius, J. Flossdorf, M. R. Kula Chem. Ber. 1975, 108, 3079).

The syntheses of cyclooctylglycine, 4-isopropylcyclohex-1-yl-alanine, 4-methylcyclohex-1-ylalanine and 4-methylcyclohex-1-ylglycine were carried out via the corresponding ethyl 2-formylaminoacrylate (U. Schöllkopf and R. Meyer, Liebigs Ann. Chem. 1977, 1174) starting from ethyl isocyanoacetate using the respective carbonyl compounds cyclooctanone, 2-norbornanone, 1-formyladamantane, 1-formyl-1-methylcyclohexane, 1-formyl-4-isopropylcyclohexane, 1-formyl-4-methylcyclohexane and 4-methylcyclohexanone according to the following general procedures:

General working procedure for the synthesis of ethyl 2-formylaminoacrylates.

The solution of 100 mmol of ethyl isocyanoacetate in 50 ml of THF was added dropwise at 0 to -10°C to 100 mmol of potassium tert-butoxide in 150 ml of THF. After 15 min, 100 mmol of the appropriate carbonyl compound in 50 ml of THF were added, the reaction mixture was slowly allowed to rise to RT and the solvent was stripped off on a rotary evaporator. The residue was mixed with 50 ml of water, 100 ml of acetic acid and 100 ml of DCM and the product was extracted with DCM. The DCM phase was dried over Na_2SO_4 and the solvent was stripped off on a rotary evaporator. If necessary, the products obtained in almost pure form were further purified by column chromatography on silica gel (eluent: mixtures of ether/petroleum ether).

General procedure for the synthesis of the amino acid hydrochlorides starting from the ethyl 2-formylaminoacrylates

100 mmol of the ethyl 2-formylaminoacrylate were hydrogenated until reaction was complete using Pd/C (10%)/hydrogen in 200 ml of glacial acetic acid. The catalyst was then filtered off, the acetic acid was removed as extensively as possible on the rotary evaporator and the residue was heated to reflux for 5 h in 200 ml of semiconcentrated hydrochloric acid. The hydrochloric acid was stripped off on the rotary evaporator, and the product was dried at 50°C in vacuo and washed several times with ether. The hydrochlorides were obtained as slightly colored crystals.

Starting from 18.9 g (150 mmol) of cyclooctanone, 25.0 g of cyclooctylglycine hydrochloride were obtained. Starting from 16.5 g (150 mmol) of 2-norbornanone, 26.6 g of 2-norbornylglycine hydrochloride were obtained. Starting from 19.7 g (120 mmol) of 1-formyladamantane, 26.0 g of adamantylalanine hydrochloride were obtained. Starting from 12.6 g (100 mmol) of 1-formyl-1-methyl-cyclohexane, 16.6 g of γ-methylcyclohexylalanine hydrochloride were obtained. Starting from 16.8 g (150 mmol) of 4-methylcyclohexanone, 25.9 g of 4-methylcyclohexylglycine hydrochloride were obtained. Starting from 15 g of trans-1-formyl-4-methylcyclohexane, 18 g of trans-4-methylcyclo-hex-1-yl-alanine hydrochloride were obtained. Starting from 9 g of 3,3-dimethyl-1-formylcyclohexane, 10 g of 3,3-dimethylcyclo-hex-1-ylalanine hydrochloride were obtained.

The aldehyde needed for the synthesis, 1-formyl-3,3-dimethyl-cyclohexane, was prepared following Moskal and Lensen (Rec. Trav. Chim. Pays-Bas 1987, 106, 137-141):

A solution of n-butyllithium in n-hexane was added dropwise in the course of 10 min at -60°C to a stirred solution of diethyl isocyanomethyl phosphonate (17 ml, 105 mmol) in 280 ml of anhydrous diethyl ether. The resulting suspension was stirred at -60°C for 15 min. and treated in the course of 10 min with a solution of 3,3-dimethylcyclohexanone (13 g, 105 mmol) in 100 ml of anhydrous diethyl ether, the temperature being kept below -45°C. The reaction mixture was allowed to come to 0°C and was stirred at this teperature for 90 min., and 150-200 ml of 38% strength aqueous hydrochloric acid were cautiously added. To complete the hydrolysis, the mixure was vigorously stirred at room temperature for 15 h. The organic phase was separated off and washed with 200 ml each of water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution. It was dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to remove the solvents. The resulting residue was employed without further purification as a starting material for the synthesis of the amino acid.

Preparation of cycloheptylglycine, cyclopentylglycine, 4-isopropylcyclohexylglycine and 3,3-dimethylcyclohexylglycine

These amino acids were prepared by reaction of cycloheptanone, cyclopentanone, 4-isopropylcyclohexanone or 3,3-dimethylcyclo-hexanone with ethyl isonitriloacetate according to a procedure of H.J. Prätorius (H.J. Prätorius, J. Flossdorf, M. Kula, Chem. Ber. 1985, 108, 3079).

Preparation of H–D,L–Chea–OH

4.0 g of cycloheptylmethyl methanesulfonate (19.39 mmol), prepared from cycloheptylmethanol and methanesulfonyl chloride, were heated to reflux in an inert gas atmosphere for 10 h with 4.9 of benzophenone imine glycine ethyl ester (18.47 mmol), 8.9 g of dry finely powdered potassium carbonate (64.65 mmol) and 1 g of tetrabutylammonium bromide (3 mmol) in 50 ml of dry acetonitrile. The potassium carbonate was then filtered off, the filtrate was evaporated to dryness and the crude product was hydrolyzed directly at RT with stirring for 1.5 h using 20 ml of 2N hydrochloric acid in 40 ml of ethanol. After dilution of the reaction solution, benzophenone was extracted with ethyl acetate in the acidic range, then H–D,L–Chea–OEt was extracted with DCM in the alkaline range (pH = 9), and the solution was dried over magnesium sulfate and concentrated in a rotary evaporator. Yield 3.7 g ≙ 95% of theory.

The amino acids mentioned were converted into the in each case Boc-protected form according to generally known processes using di-tert-butyl dicarbonate in water/dioxane and then recrystallized from ethyl acetate/hexane mixtures or purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether mixtures).

The Boc-protected amino acids were employed as B units according to Scheme I.

As B units, the amino acids mentioned were in some cases also converted into the corresponding benzyl esters and linked to the appropriately protected A units. In the case of compounds having a still free NH function, this was then protected by a Boc group, the benzyl ester group was removed by hydrogenation and the unit A-B-OH was purified by crystallization, salt precipitation or column chromatography. This route is described by way of example for tBuOOC–CH_2–(Boc)(D)Cha–OH below.

Synthesis of D–cyclohexylalanine benzyl ester

A suspension of 100 g (481 mmol) of D-cyclohexylalanine hydrochloride, 104 g (962 mmol) of benzyl alcohol and 109.7 g (577 mmol) of p-toluenesulfonic acid monohydrate in 2200 ml of toluene was slowly heated to reflux in a water separator. In a temperature range from 80-90°C, evolution of hydrogen chloride and the dissolution of the suspension to give a clear solution was observed. When water no longer separated (about 4 h), 500 ml of toluene were distilled off, the reaction mixture was allowed to

cool overnight, and the resulting residue was filtered off and washed twice with 1000 ml each of hexane. The resulting residue (195 g) was then suspended in 2000 ml of dichloromethane, treated with 1000 ml of water and adjusted to pH 9-9.5 with stirring by successive addition of 50% strength sodium hydroxide solution. The organic phase was separated off, washed twice with 500 ml each of water, dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated, whereby 115 g (94%) of the title compound were obtained as a pale oil.

N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylalanine benzyl ester

115 g (440 mmol) of D-cyclohexylalanine benzyl ester were dissolved in 2000 ml of acetonitrile, treated at room temperature with 607.5 g (4.40 mmol) of potassium carbonate and 94.3 g (484 mmol) of tert-butyl bromoacetate and stirred at this temperature for 3 days. The carbonate was filtered off and washed with acetonitrile, the mother liquor was concentrated (30°C, 20 mbar), the residue was taken up in 1000 ml of methyl tert-butyl ether and the organic phase was extracted with 5% strength citric acid and saturated sodium hydrogencarbonate solution. The organic phase was dried over sodium sulfate, the drying agent was filtered off, the filtrate was concentrated and the oil obtained (168 g) was employed directly in the following reaction.

N-Boc-N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylalanine benzyl ester

The oil obtained in the previous synthesis (168 g, 447 mmol) was dissolved in 1400 ml of acetonitrile, treated with 618 g (4.47 mmol) of potassium carbonate powder and 107.3 g (492 mmol) of di-tert-butyl dicarbonate and the mixture was stirred at room temperature for 6 days. The potassium carbonate was filtered off with suction, washed with about 1000 ml of acetonitrile and the filtrate was concentrated. 230 g of the desired product were obtained.

N-Boc-N-(tert-butyloxycarbonylmethylene)-D-cyclohexylalanine cyclohexylammonium salt

115 g of N-Boc-N-(tert-butyloxycarbonylmethylene)-D-cyclohexylalanine benzyl ester were dissolved in 1000 ml of pure ethanol and hydrogenated at normal pressure with hydrogen for 2 h at 25-30°C in the presence of 9 g of 10% strength Pd on active carbon. After filtration and removal of the solvent in a rotary

evaporator, 100 g (260 mmol) of a yellow oil were obtained, which was taken up in 1600 ml of acetone and heated to reflux. The heating bath was removed and a solution of 27 g (273 mmol) of cyclohexylamine in acetone was added rapidly through a dropping funnel. On cooling the reaction mixture to room temperature, the desired salt crystallized out. The solid was filtered off, washed with 200 ml of acetone and recrystallized once more from acetone for final purification. After drying the residue in a vacuum drying oven at 30°C, 70.2 g of the desired salt were obtained as a white powder.

N-Boc-N-(tert-butyloxycarbonylmethylene-D-cyclohexylglycine cyclohexylammonium salt was prepared in an analogous manner from cyclohexylglycine as starting material.

N-Boc-N-(tert-butyloxycarbonylethylene)-D-cyclohexylalanine cyclohexylammonium salt

a) tert-Butyl 3-bromopropionate

16.64 g (109 mmol) of bromopropionic acid, 150 ml of condensed 2-methylpropene and 2 ml of concentrated sulfuric acid were added at -30°C in a nitrogen countercurrent to a glass vessel suitable for an autoclave, the vessel was firmly sealed and the mixture was stirred at room temperature for 72 h. For working-up, the reaction vessel was again cooled to -30°C and the reaction solution was cautiously poured into 200 ml of an ice-cold, saturated sodium hydrogencarbonate solution. Excess 2-methylpropene was allowed to evaporate with stirring, the residue was extracted three times with 50 ml each of dichloromethane, the combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated in a water-jet vacuum. The oil residue was purified by column chromatography (eluent N-hexane, later N-hexane/diethyl ether 9:1). 18.86 g of the title compound were obtained.

b) N-(tert-Butyloxycarbonylethylene)-D-cyclohexylalanine benzyl ester

49.4 g (189 mmol) of D-cyclohexylalanine benzyl ester were dissolved in 250 ml of acetonitrile, treated at room temperature with 31.6 g (151 mmol) of tert-butyl bromopropionate and the mixture was refluxed for 5 days. The resulting precipitate was filtered off, washed repeatedly with acetonitrile, the filtrate was concentrated in a water-jet vacuum, the residue was taken up in 350 ml of

dichloromethane and the organic phase was extracted with 5% strength citric acid and saturated sodium hydrogencarbonate solution. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated. The oily residue was purified by column chromatography (eluent: dichloromethane, later dichloromethane/methanol 95:5). A slightly impure oil was obtained, which was employed directly in the following reaction.

c) N-Boc-N-(tert-butyloxycarbonylethylene)-D-cyclohexylalanine benzyl ester

The oil obtained in the preceding synthesis (30 g, max. 70 mmol) was dissolved in 150 ml of acetonitrile, treated with 28 ml (160 mmol) of diisopropylethylamine and 19.2 (88 mmol) of di-tert-butyl dicarbonate and stirred at room temperature for 3 days. The reaction mixture was concentrated on the rotary evaporator in a water-jet vacuum, the residue was taken up in n-hexane and washed five times with 3 ml each of a 5% strength citric acid solution, the combined organic phases were dried over sodium sulfate, the drying agent was filtered off, the filtrate was concentrated and the residue was subjected to purification by column chromatography (eluent: hexane/ethyl acetate 95:5). 32.66 g (64 mmol) of the desired product were obtained.

d) N-Boc-N-(tert-butyloxycarbonylethylene-D-cyclohexylalanine cyclohexylammonium salt

32.66 g (64 mmol) of N-Boc-N-(tert-butyloxycarbonylethylene)-D-cyclohexylalanine benzyl ester were dissolved in 325 ml of pure ethanol and hydrogenated at 25 to 30°C with hydrogen at normal pressure for 14 h in the presence of 3 g of 10% strength Pd on active carbon. After filtration of the solution through Celite®, washing with ethanol and removal of the solvent in a rotary evaporator, 26.7 g of a yellow oil were obtained, which was taken up in acetone and heated to reflux. The heating bath was removed and the solution of 7 g (70 mmol) of cyclohexylamine in acetone was added rapidly through a dropping funnel. On cooling the reaction mixture to room temperature, the desired salt crystallized out. The solid was filtered off, washed with 25 ml of acetone and recrystallized once more from acetone for final purification. After drying the residue in a vacuum drying oven at 30°C,

26.6 g (54 mmol) of the desired salt were obtained as a white powder.

N-Boc-N-(tert-butyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroproline:

a) N-Boc-Pyr-OH (5 g, 23.45 mmol) was dissolved in MeOH (50 ml) and treated with HCl in dioxane (4N, 30 ml). The mixture was then heated under reflux for 12 h. The solvent was removed in a rotary evaporator and H-Pyr-OMe hydrochloride was obtained as the product. Yield: 3.84 g (100%).

b) N-(t-BuO_2C-CH_2)-N-Boc-(D)-Cha-OH (8 g, 20.75 mmol) was dissolved in dichloromethane (75 ml) and treated at -10°C with ethyldiisopropylamine (15.5 ml, 89.24 mmol). After storing at this temperature for 5 min., a solution of H-Pyr-OMe hydrochloride (3.4 g, 20.75 mmol) in dichloromethane (25 ml) was added dropwise. A solution of propanephosphonic anhydride in ethyl acetate (50% strength, 20 ml, 26.96 mmol) was then added dropwise and the mixture was stirred at -10 to 0°C for 2 h. The batch was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution (2 x 80 ml, 5% strength citric acid solution (2 x 15 ml) and saturated sodium chloride solution (1 x 20 ml). The organic phase was dried over sodium sulfate and the solvent was removed in a rotary evaporator. The crude product was purified by means of flash chromatography (silica gel, dichloromethane/methanol 95/5). Yield: 6.2 g (60%).

c) N-(t-BuO_2C-CH_2)-N-Boc-(D)-Cha-Pyr-OMe (5.5 g, 11.12 mmol) was dissolved in dioxane (40 ml), treated with sodium hydroxide solution (1N, 22.2 ml, 22.24 mmol) and stirred at room temperature for 2 h. The dioxane was removed in a rotary evaporator, and the aqueous phase was washed with ethyl acetate and acidified to pH 1 to 2 with potassium hydrogensulfate solution (20% strength). The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over sodium sulfate. Yield: 5 g (94%), colorless foam. Recrystallization from n-hexane saturated with water afforded colorless crystals (m.p. = 158 to 160°C).

N-Boc-N-(tert-butyloxycarbonylmethylene)-(D)-cyclohexylglycyl-3,4-dehydroproline

This compound was prepared from N–Boc–N–(tert–butyloxycarbonyl-methylene)–(D)–cyclohexylglycine and 3,4–dehydroproline methyl ester in an analogous manner.

The (L)3,4–dehydroproline employed as the D unit can be obtained commercially; the (D,L)-4,5–dehydropipecolic acid can be prepared according to A. Burgstahler, C.E. Aiman J. Org. Chem. 25 (1960), 489 or C. Herdeis, W. Engel Arch. Pharm 326 (1993), 297 and then converted into Boc–(D,L)–Dep–OH using $(Boc)_2O$.

The synthesis of 3–(6–cyano)picolylamine has been described in WO 96/25426 and WO 96/24609.

3–(6–Cyano)picolylamine

The preparation of this component was carried out as described in WO 96/25426 and WO 96/24609.

Example 1:
N–(tert-butoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide

A suspension of 1.22 g (17.6 mmol) of hydroxylamine hydrochloride in 50 ml of ethanol was treated with 1.3 g of conc. ammonia, stirred for 30 min. and the deposited precipitate (ammonium chloride) was filtered off with suction. 4.3 g (8.9 mmol) of N–(tert-butoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–cyano–3-picolyl)amide (WO 96/25426, Example 93, stage a) were then added to the alcoholic hydroxylamine solution and it was allowed to stand at room temperature for one hour. According to TLC (eluent: dichloromethane/ethanol = 9:1 or dichloromethane/methanol/conc. ammonia = 45:5:0.3), starting material was no longer detectable. After distilling off the solvent in vacuo, the residue was dissolved in 100 ml of dichloromethane, and the solution was washed with water and aqueous sodium hydrogencarbonate solution and dried over sodium sulfate. After concentration, 4.1 g (87%) of an amorphous residue remained.
FAB-MS $(M+H^+)$: 529

Example 2:
N–(Hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydro-prolyl–(6–hydroxyamidino–3-picolyl)amide hydrochloride

3.5 g (6.6 mmol) of N–(tert-butoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)-amide (see Ex. 1) were dissolved in 15 ml of dichloromethane,

treated with 25 ml of a 4N solution of hydrogen chloride in dioxane and allowed to stand at room temperature overnight. After distilling off the solvent in vacuo (toward the end with addition of toluene), the amorphous residue was digested repeatedly with diethyl ether. After drying, 3.1 g (90% of theory) of a white amorphous powder remained.
FAB-MS ($M+H^+$): 473

Example 3:
N–(Ethoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide

2.5 g (5.3 mmol) of N–(hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide hydrochloride (see Ex. 2) were dissolved in 50 ml of dry ethanol, treated with 3 ml of a 4N solution of hydrogen chloride in dioxane, refluxed for 4 hours and allowed to stand at room temperature for 2 days.
After distilling off the solvent in vacuo at a bath temperature of 35°C, the residue was digested repeatedly with diethyl ether, then taken up in ethyl acetate and extracted with saturated sodium hydrogencarbonate solution. The organic phase was dried over sodium sulfate and concentrated, and the residue was purified by column chromatography (eluent dichloromethane/ethanol = 9:1, toward the end 4:1). After distilling off the solvent, 1.85 g (70% of theory) of a white amorphous powder remained,
FAB-MS ($M+H^+$): 501

Example 4:
N–(Methoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide

This compound was prepared analogously to Example 3, the residue digested with ether first being dissolved in methanol and converted into the acetic acid salt by means of ion exchanger before it was purified by column chromatography (eluent dichloromethane/methanol = 9:1).
FAB-MS ($M+H^+$): 487

Example 5:
N–(Isopropyloxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide

This compound was prepared analogously to Example 3, the starting material N–(hydroxycarbonylmethylene)- (D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–hydroxyamidino–3-picolyl)amide hydrochloride (see Ex. 2) being dissolved in isopropanol and

hydrogen chloride being introduced. The work-up and purification was carried out analogously to Example 4.
FAB-MS ($M+H^+$): 515

Example 6:
N-(Benzyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and benzyl alcohol.
FAB-MS ($M+H^+$): 563

Example 7:
N-(Ethyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[(6-amidino)-3-picolylamide] hydrochloride

HO_2C-CH_2-(D)-Cha-Pyr-NH-3-(6-am)-pico (4.93 g, 10 mmol; preparation: WO 96/25426, Example 93) was dissolved in 60 ml of ethanol, treated with HCl in ether (4.5N, 15 ml) and stirred at 60°C for 6 h. As according to TLC (methylene chloride/methanol/acetic acid (50% strength in water): 35/15/7) the conversion was still not complete, a further 25 ml of 4.5N hydrogen chloride in ether and 50 ml of ethanol were added and the mixture was stirred at 60°C again for 5 h. After concentrating the reaction mixture in vacuo in a rotary evaporator, it was codistilled a number of times with ethanol and ether in order to remove adhering hydrochloric acid. The product was then washed by stirring in a little acetone/methylene chloride, and the residue was filtered off with suction and dried in vacuo. 5.4 g of the title compound were obtained as a white, hygroscopic solid substance.
FAB-MS ($M+H^+$): 485

Example 8:
N-(Methyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[(6-amidino)-3-picolylamide] hydrochloride

This compound was prepared analogously to Example 7 by esterification of HO_2C-CH_2-(D)-Cha-Pyr-NH-3-(6-am)-pico with methanol.
FAB-MS (M+H+): 471

Example 9:
N-(n-Propyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-[(6-amidino)-3-picolylamide] hydrochloride

This compound was prepared analogously to Example 7 by esterification of HO_2C-CH_2-(D)-Cha-Pyr-NH-3-(6-am)-pico with n-propanol.
FAB-MS (M+H+): 499

Example 10:
N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxy-amidino-3-picolyl)amide

a) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-aminothiocarbonyl-3-picolyl)amide

t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-CN)-pico (WO 96/25426, Ex. 93, stage b) was reacted with hydrogen sulfide in pyridine/triethylamine to give the corresponding thioamide t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-$CSNH_2$)-pico according to WO 96/25426, Ex. 93, stage c).

b) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-S-methyliminothiocarbonyl-3-picolyl)-amide hydroiodide

The product t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-$CSNH_2$)-pico obtained from a) was reacted with methyl iodide to give t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(SCH_3))-pico x HI analogously to WO 96/25426, Ex. 93, Stage d.

c) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide

O-Methylhydroxylamine hydrochloride (0.9 g, 8.1 mmol) was dissolved in 30 ml of methanol and converted into the corresponding acetic acid salt by means of an ion exchanger (Fluka: acetate on polymeric support, 3.0 mmol of acetate per g). t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(SCH_3))-pico x HI (4.8 g, 6.2 mmol; see b) was added to this methanolic solution and the reaction mixture was stirred at room temperature overnight. After concentrating in vacuo, the residue was taken up in 200 ml of ethyl acetate, washed three times with 30 ml each of water, twice with 20 ml each of 20% strength sodium hydrogensulfate solution and once with 30 ml of saturated sodium chloride solution and then purified by

column chromatography on silica gel, 0.9 g of the desired product being isolated.

d) N–(Hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–methoxyamidino–3–picolyl)amide

The product t–BuO_2C–CH_2–(Boc)–(D)–Cha–Pyr–NH–3–(6–C=NH($NHOCH_3$))–pico (0.9 g, 0.7 mmol) obtained according to c) was dissolved in 10 ml of absolute dioxane, cooled to 0°C and treated with 5 ml of a 4N solution of hydrogen chloride in dioxane. The mixture was stirred at room temperature for 6 h with exclusion of moisture, then dissolved in water and subjected to salt exchange by means of an acetate exchanger and the aqueous phase was freeze-dried. 0.38 g of the title compound was obtained as a white powder. FAB-MS (M+H+): 487

Example 11:
N–(Methoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–methoxy-amidino–3-picolyl)amide

A solution of 1.5 g (2.9 mmol) of N–(hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–methoxyamidino–3–picolyl)amide (see Ex. 10 d) in methanol was treated with a 4N solution of hydrogen chloride in dioxane and stirred at room temperature for 2 days. It was concentrated, the residue was codistilled twice with diethyl ether in order to remove excess acid and the crude product was purified by column chromatography. FAB-MS ($M+H^+$): 501

Example 12:
N–(Isopropyloxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–methoxyamidino–3-picolyl)amide

This compound was prepared analogously to Example 11 by esterification of N–(hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–(6–methoxyamidino–3-picolyl)-amide (see Ex. 10d) with isopropanol. FAB-MS ($M+H^+$): 529

Example 13:
N-(n-Octyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and n-octanol.
FAB-MS ($M+H^+$): 585

Example 14:
N-(c-Hexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 3 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and c-hexanol.
FAB-MS ($M+H^+$): 555

Example 15:
N-(Neopentyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 3 from N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and neopentyl alcohol.
FAB-MS ($M+H^+$): 543

Example 16:
N-(Methoxyethoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide-hydrochloride (see Ex. 2) and ethylene glycol monomethyl ether.
FAB-MS ($M+H^+$): 531

Example 17:
N-(O-Methyldiethoxyoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and diethylene glycol monomethyl ether.
FAB-MS ($M+H^+$): 575

Example 18:
N-(Cyclohexylmethyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide-hydrochloride (see Ex. 2) and cyclohexylmethanol, the residue digested with ether being filtered off and purified by means of reversed phase HPLC.
FAB-MS ($M+H^+$): 569

Example 19:
N-(Cyclooctyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and cyclooctanol. As the purification by column chromatography using the eluent dichloromethane/methanol = 9:1 failed, a second purification was carried out (eluent ethyl acetate) by means of MPLC (silica gel). The title compound was obtained as a white powder.
FAB-MS ($M+H^+$): 583

Example 20:
N-(trans-4-Methylcyclohexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)-amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and trans-4-methylcyclohexanol. As the purification by column chromatography using the eluent dichloromethane/methanol = 9:1 and 95:5 failed, a third purification was carried out (eluent ethyl acetate) by means of MPLC (silica gel). The title compound was obtained as a white powder.
FAB-MS ($M+H^+$): 569

Example 21:
N-(n-Hexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and n-hexanol, the purification by column chromatography being carried out on silica gel (MPLC; eluent ethyl acetate/n-hexane = 7:3).
FAB-MS ($M+H^+$): 557

Example 22:
N-(c-Pentyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and c-pentanol, the purification by column chromatography being carried out on silica gel (MPLC; eluent ethyl acetate/n-hexane = 1:1).
FAB-MS ($M+H^+$): 541

Example 23:
N-(4-Methoxycyclohexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 4 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide hydrochloride (see Ex. 2) and 4-methoxycyclohexanol, the purification by column chromatography being carried out silica gel (MPLC; eluent ethyl acetate/methanol = 99:1, with an increase in the proportion of methanol of 0.1% per minute). The title compound was obtained as a cis/trans mixture (according to HPLC the ratio of the two isomers was 29:71).
FAB-MS ($M+H^+$): 585

Example 24:
N-(1,1,2-Trimethylpropyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

a) 1,1,2-Trimethylpropyl bromoacetate

3.5 ml (1.1 equivalents) of pyridine and, at -5°C, 7.9 g (39 mmol) of bromoacetyl bromide were added at room temperature to a solution of 4.0 g (39 mmol) of 2,3-dimethyl-2-butanol in 20 ml of dichloromethane. During the addition of the bromide, which proceeded in a strongly exothermic manner, a pale precipitate was formed. During the course of this, the temperature rose to 20°C. The mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate and extracted three times with 5 ml each of saturated sodium chloride solution. The ethyl acetate phase was dried over magnesium sulfate and concentrated, and the residue obtained was employed in the next reaction without further purification.

b) N-(1,1,2-Trimethylpropyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-cyano-3-picolyl)amide

30 ml of a 4N solution of hydrogen chloride in dioxane was added at -5°C to a solution of 14.1 g (29.3 mmol) of Boc-(D)-Cha-Pyr-NH-3-(6-CN)-pico (WO 96/25426, Ex. 32, stage d) in 30 ml of dioxane. The mixture was stirred at room temperature for 3 hours and concentrated. The residue was taken up a total of three times in dichloromethane and concentrated again in order to remove the excess hydrogen chloride. After the residue had been taken up in 50 ml of ethyl acetate and had been treated with 200 ml of diethyl ether, the product precipitated. It was filtered off and washed with diethyl ether. After drying, 12.0 g (98%) of the compound H-(D)-Cha-Pyr-NH-3-(6-CN)-pico were obtained as the hydrochloride.

2.3 g (5.5 mmol) of H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl were dissolved in 20 ml of dichloromethane, and the solution was treated at room temperature with 7.6 g (54.7 mmol) of potassium carbonate and dropwise at -5°C with 1.22 g (5.5 mmol) of 1,1,2-trimethylpropyl bromoacetate. It was allowed to come to room temperature and stirred for 3 days. The reaction mixture was concentrated in vacuo in a rotary evaporator, taken up in ethyl acetate, and the solution was washed three times with a little water and once with saturated sodium chloride solution. The organic phase was dried and concentrated. The residue was purified by column chromatography (eluent dichloromethane/methanol = 9:1) by means of MPLC (silica gel). 1.82 g (64%) of the title compound were obtained as a white powder.
FAB-MS ($M+H^+$): 524

c) N-(1,1,2-Trimethylpropyloxycarbonylethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

0.17 g (1.32 mmol) of diisopropylethylamine and 73 mg (1.05 mmol) of hydroxylamine hydrochloride were added at room temperature to a solution of 460 mg (0.88 mmol) of the compound obtained in b) in 10 ml of dichloromethane. The mixture was stirred at room temperature for 4 hours, diluted with dichloromethane and extracted twice with 5 ml each of 5% strength citric acid solution. The organic phase was dried and concentrated. The residue was purified by column chromatography by means of reverse phase HPLC. The title compound was obtained as a white powder.
FAB-MS ($M+H^+$): 557

Example 25:
N-(2-Methyl-1,3-dioxan-5-yloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 24 starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and 2-methyl-1,3-dioxan-5-ol, the hydroxylamine addition being carried out in acetonitrile and the purification by column chromatography on silica gel (MPLC; eluent ethyl acetate/methanol = 99:1, with an increase in the proportion of methanol of 0.1% per minute). The title compound was obtained as a white powder.
FAB-MS ($M+H^+$): 573

Example 26:
N-(1-Isopropyl-2-methylpropyloxycarbonylmethylene)-(D)-cyclohexyl alanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 24 starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and 2,4-dimethyl-3-pentanol, the hydroxylamine addition being carried out in acetonitrile and the purification by column chromatography on silica gel (MPLC; eluent ethyl acetate/methanol = 99:1, with an increase in the proportion of methanol of 0.1% per minute). The title compound was obtained as a white powder.
FAB-MS ($M+H^+$): 571

Example 27:
N-(2-Indanyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 25 starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and 2-indanol.
FAB-MS $(M+H^+)$: 589

Example 28:
N-(1-Isobutyl-3-methyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 25 starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and 2,6-dimethyl heptan-4-ol.
FAB-MS $(M+H^+)$: 599

Example 29:
N-[4-Oxo-4-(1-pyrrolidinyl)butyloxycarbonylmethylene]-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

a) 4-Oxo-4-(1-pyrrolidinyl)-1-butanol

A mixture of 7.1 g (82 mmol) of γ-butyrolactone and 11.7 g (164.5 mmol) of pyrrolidine was stirred at room temperature for 3 hours. The pyrrolidine was distilled off in vacuo in a rotary evaporator to the greatest possible extent, and the residue was dissolved in toluene a number of times and concentrated again in order to remove traces of the base. The product obtained was employed in the following reaction without purification.

b) 4-Oxo-4-(1-pyrrolidinyl)butyl bromoacetate

The product obtained a) was reacted with bromoacetyl bromide analogously to Example 24a), 4-dimethylaminopyridine being employed as a base instead of pyridine.

The title compound was obtained analogously to Example 24 starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and the 4-oxo-4-(1-pyrrolidinyl)butyl bromoacetate prepared in b).
FAB-MS $(M+H^+)$: 612

Example 30:

N-[2-(Cyclohexylamino)-2-oxoethyloxycarbonylmethylene]-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)-amide

a) N-Cyclohexyl-2-hydroxyacetamide

A mixture of 1.2 g (10 mmol) of 1,4-dioxane-2,5-dione and 4.0 g (40 mmol) of cyclohexylamine was stirred at a temperature of 100°C for 3 hours. The cyclohexylamine was distilled off in vacuo in a rotary evaporator to the greatest possible extent, and the residue was dissolved a number of times in toluene and concentrated again in order to remove traces of the base. The product obtained was dissolved in diethyl ether and added dropwise to petroleum ether, a precipitate being deposited. The precipitate was filtered off and employed in the following reaction without further purification.

b) 2-(Cyclohexylamino)-2-oxoethyl bromoacetate

The product obtained in a) was reacted with bromoacetyl bromide analogously to Example 24a), 4-dimethylaminopyridine being employed as base instead of pyridine.

Analogously to Example 24, the title compound was obtained starting from H-(D)-Cha-Pyr-NH-3-(6-CN)-pico x HCl and the 2-(cyclohexylamino)-2-oxoethyl bromoacetate prepared in b). FAB-MS ($M+H^+$): 612

Example 31:

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-{5-[2-(1,2,4-oxadiazol-3-yl-5-on)]-pyridyl}methylamide hydrochloride

a) N-(tert-butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-hydroxyamidino-3-picolyl)amide

11.9 g (20 mmol) of N-(tert-butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-cyano-3-picolyl)-amide (WO 96/25426, Example 93, Stage b), 2.78 g (40 mmol) of hydroxylamine hydrochloride and 4.65 g (36 mmol) of diisopropylethylamine were dissolved in 100 ml of ethanol and heated at 55-60°C for 5 hours. The solution was concentrated in vacuo, the residue was taken up in 100 ml of ethyl acetate and the mixture was washed twice with saturated sodium chloride solution. After drying and distilling off the

solvent, 11.3 g (90% of theory) of slightly yellowish, amorphous residue remained.

b) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexyl-alanyl-3,4-dehydroprolyl-{5-[2-(1,2,4-oxadiazol-3-yl-5-one)]-pyridyl}methylamide

10.2 g (16.2 mmol) of the above amidoxime were dissolved in 60 ml of pyridine and, after addition of 2.9 g (17.9 mmol) of carbonyldiimidazole, heated under reflux for 3 hours. The pyridine was distilled off in vacuo, the residue was taken up in methyl tert-butyl ether, and the solution was washed with 5% strength citric acid solution and finally with saturated sodium chloride solution. After drying and distilling off the solvent, 10 g (94% of theory) of amorphous residue remained).

c) N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-{5-[2-(1,2,4-oxadiazol-3-yl-5-one)]-pyridyl}-methylamide hydrochloride

10 g (15.3 mmol) of the compound obtained in b) were dissolved in 80 ml of glacial acetic acid, treated with 80 ml of a 4N solution of hydrogen chloride in dioxane and allowed to stand at room temperature overnight.

After distilling off the solvent in vacuo (toward the end with addition of toluene), the amorphous residue was purified by column chromatography (eluent: ethanol/25% strength ammonia = 50:2.5). The residue was dissolved in a mixture of water and dioxane (ratio 3:7), treated with one equivalent of 32% strength hydrochloric acid and concentrated to dryness. The residue was digested with acetonitrile and then filtered off with suction. 3.9 g (48% of theory) of a white powder were isolated;
FAB-MS ($M+H^+$): 499

Example 32:
N-(Methoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydro-prolyl-{5-[2-(1,2,4-oxadiazol-3-yl-5-one)]-pyridyl}methylamide hydrochloride

1.9 g (3.6 mmol)of N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-{5-[2-(1,2,4-oxadiazol-3-yl-5-one)]-pyridyl}methylamide hydrochloride (see Example 31) were dissolved in 100 ml of methanol and, with addition of 10 ml of a

4N solution of hydrogen chloride in dioxane, heated under reflux for 8 hours.

The residue was digested with acetonitrile and then filtered off with suction. 1.65 g (85% of theory) of a white powder were isolated;
FAB-MS ($M+H^+$): 513

Example 33:
N-(Neopentyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide

This compound was prepared analogously to Example 7 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide hydrochloride (Preparation: WO 9625426, Example 93) and neopentyl alcohol.
FAB-MS ($M+H^+$): 527

Example 34:
N-(n-Hexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide

This compound was prepared analogously to Example 7 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide hydrochloride (Preparation: WO 9625426, Example 93) and n-hexanol.
FAB-MS ($M+H^+$): 541

Example 35:
N-(c-Hexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide

This compound was prepared analogously to Example 7 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide hydrochloride (Preparation: WO 9625426, Example 93) and c-hexanol.
FAB-MS ($M+H^+$): 539

Example 36:
N-(methoxyethoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide

This compound was prepared analogously to Example 7 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide hydrochloride (Preparation: WO 9625426, Example 93) and ethylene glycol monomethyl ether.

FAB-MS ($M+H^+$): 515

Example 37:
N-(O-Methyldiethoxyoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide

This compound was prepared analogously to Example 7 from N-(hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-amidino-3-picolyl)amide hydrochloride (Preparation: WO 9625426, Example 93) and diethylene glycol monomethyl ether.
FAB-MS ($M+H^+$): 559

Example 38:
N-(Methoxyethoxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide

This compound was prepared starting from N-(tert-butoxycarbonyl-methylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide (see Ex. 10c).

The removal of the protective groups and the transesterification/esterification of the carboxyl function in t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH($NHOCH_3$))-pico was achieved by treating with a 4N solution of hydrogen chloride in dioxane and a large excess of ethylene glycol monomethyl ether. The work-up and purification of the compound obtained was carried out analogously to Ex. 11.
FAB-MS ($M+H^+$): 545

Example 39:
N-(n-Octyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide

This compound was prepared starting from N-(tert-butoxycarbonyl-methylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide (see Ex. 10c).

The removal of the protective groups and the transesterification/esterification of the carboxyl function in t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH($NHOCH_3$))-pico was achieved by treating with a 4N solution of hydrogen chloride in dioxane and a large excess of n-octanol. The work-up and purification of the compound obtained was carried out analogously to Ex. 11.
FAB-MS ($M+H^+$): 599

Example 40:
N-(c-Hexyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide

This compound was prepared starting from N-(tert-butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-methoxyamidino-3-picolyl)amide (see Ex. 10c).
The removal of the protective groups and the transesterification/esterification of the carboxyl function in t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH($NHOCH_3$))-pico was achieved by treating with a 4N solution of hydrogen chloride in dioxane and a large excess of cyclohexanol. The work-up and purification of the compound obtained was carried out analogously to Ex. 11.
FAB-MS ($M+H^+$): 569

Example 41:
N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-allyloxyamidino-3-picolyl)amide

a) N-(tert-butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-aminothiocarbonyl-3-picolyl)amide
t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-CN)-pico (WO 96/25426, Ex. 93, stage b) was reacted with hydrogen sulfide in pyridine /triethylamine to give the corresponding thioamide t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-$CSNH_2$)-pico according to WO 96/25426, Ex. 93, Stage c).

b) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-S-methyliminothiocarbonyl-3-picolyl)-amide hydroiodide

The product t-BuO2C-CH2-(Boc)-(D)-Cha-Pyr-NH-3-(6-$CSNH_2$)-pico obtained from a) was reacted with methyl iodide to give t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(SCH_3))-pico x HI analogously to WO 96/25426, Ex. 93, Stage d).

c) N-(tert-Butoxycarbonylmethylene)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-allyloxyamidino-3-picolyl)amide

O-Allylhydroxylamine hydrochloride (0.93 g, 7.0 mmol) were dissolved in 20 ml of methanol and converted into the corresponding acetic acid salt by means of an ion exchanger (Fluka: acetate on polymeric support, 3.0 mmol of acetate per g). t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(SCH_3))-pico x HI (4.5 g, 5.8 mmol; see b) was added to this methanolic solution and the reaction mixture was stirred at room

temperature overnight. After concentrating in vacuo, the residue was taken up in ethyl acetate, washed three times with 30 ml each of water, twice with 20 ml each of 20% strength sodium hydrogensulfate solution and once with 30 ml of saturated sodium chloride solution and then purified by column chromatography on silica gel, 2.1 g of the desired product being isolated.

d) N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-allyloxyamidino-3-picolyl)amide

The product t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(NHO-allyl))-pico (2.1 g, 3.1 mmol) obtained as in c) was dissolved in 5 ml of absolute dioxane, cooled to 0°C and treated with 5 ml of a 4N solution of hydrogen chloride in dioxane. The mixture was stirred at room temperature for 6 h with exclusion of moisture and concentrated, then the residue was dissolved in water, the solution was subjected to salt exchange by means of an acetate exchanger and the aqueous phase was freeze dried. 0.69 g of the title compound was obtained as a white powder.
FAB-MS (M+H+): 513

Example 42:
N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroprolyl-(6-benzyloxyamidino-3-picolyl)amide

This compound was prepared analogously to Example 41, the product t-BuO_2C-CH_2-(Boc)-(D)-Cha-Pyr-NH-3-(6-C=NH(SCH_3))-pico x HI obtained in 41c) being reacted with O-benzylhydroxylamine (corresponding to Ex. 40 subjected to salt exchange from the hydrochloride to the acetate) at 35°C in the course of 30 min. Work-up was carried out analogously to Ex. 41. As the purification by column chromatography by means of MPLC (silica gel) using the eluent ethyl acetate/cyclohexnae = 1:1 failed, a second purification was carried out by means of MPLC (eluent ethyl acetate/cyclohexane = 3:7). 1.5 g of the title compound were obtained as a white powder. The removal of the Boc protective group and the hydrolysis of the tert-butyl ester were carried out using a solution of hydrogen chloride in diethyl ether.
FAB-MS (M+H+): 563

Example 43:
N–(Hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydro-prolyl–[6–(m-methoxy-benzyloxy)amidino–3–picolyl]amide

This compound was prepared analogously to Example 41, the product t–BuO_2C–CH_2–(Boc)–(D)–Cha–Pyr–NH–3–(6–C=NH(SCH_3))–pico x HI obtained in 41c) being reacted with O-(m-methoxybenzyl)-hydroxylamine (corresponding to Ex. 40 subjected to salt exchange from the hydrochloride to the acetate) at 35°C in the course of 30 min. Work-up was carried out analogously to Ex. 41. As the purification by column chromatography by means of MPLC (silica gel) using the eluent ethyl acetate/cyclohexnae = 1:1 failed, a second purification was carried out by means of MPLC (eluent ethylacetate/cyclohexane = 3:7). 1.5 g of the title compound were obtained as a white powder. The removal of the Boc protective group and the hydrolysis of the tert-butyl ester were carried out using a solution of hydrogen chloride in diethyl ether.
FAB-MS (M+H+): 563

Example 44:
N–(Hydroxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydroprolyl–[6-(4-chlorophenyl)hexyloxy)amidino–3-picolyl]-amide

This compound was prepared analogously to Example 41, the product t–BuO_2C–CH_2–(Boc)–(D)–Cha–Pyr–NH–3–(6–C=NH(SCH_3))–pico x HI obtained in 41 c) being reacted with O-[6-(4-chlorophenyl)hexyl]-hydroxylamine at 20°C in the course of 10 hours. The removal of the Boc protective group and the hydrolysis of the tert-butyl ester were carried out using a 4N solution of hydrogen chloride in dioxane.
FAB-MS (M+H+): 667

Example 45:
N–(Ethoxycarbonylmethylene)–(D)–cyclohexylalanyl–3,4–dehydro-prolyl–[6-(4-chlorophenyl)hexyloxy)amidino–3-picolyl]amide

This compound was prepared analogously to Example 11 by esterification of N–(hydroxycarbonylmethylene)–(D)–cyclohexyl-alanyl–3,4–dehydroprolyl–[6-(4-chlorophenyl)hexyloxy)–amidino–3-picolyl]amide (Ex. 44) with ethanol in a 4N solution of hydrogen chloride in dioxane.
FAB-MS ($M+H^+$): 695

Example 46:
N—(Hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—(p-methyl-benzyloxy)amidino—3-picolyl]amide

This compound was prepared analogously to Example 43, the product t—BuO_2C—CH_2—(Boc)—(D)—Cha—Pyr—NH—3—(6—C=NH(SCH_3))—pico x HI obtained in 41 c) being reacted with O-(p-methylbenzyl)-hydroxylamine. The removal of the Boc protective group and the hydrolysis of the tert-butyl ester were carried out using a 4N solution of hydrogen chloride in dioxane.
FAB-MS (M+H+): 577

Example 47:
N—(Ethoxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—(p-methylbenzyloxy)amidino—3-picolyl]amide

This compound was prepared analogously to Example 11 by esterification of N—(hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—(p-methylbenzyloxy)amidino—3-picolyl]amide (Ex. 46) with ethanol in a 4N solution of hydrogen chloride in dioxane.
FAB-MS ($M+H^+$): 605

Example 48:
N—(Hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—phenyloxyamidino—3-picolyl]amide

This compound was prepared analogously to Example 43, the product t—BuO_2C—CH_2—(Boc)—(D)—Cha—Pyr—NH—3—(6—C=NH(SCH_3))—pico x HI obtained in 41c) being reacted with O-phenylhydroxylamine hydrochloride in the presence of two equivalents of diisopropylethylamine. The removal of the Boc protective group and hydrolysis of the tert-butyl ester was carried out using a 4N solution of hydrogen chloride in dioxane.
FAB-MS (M+H+): 549

Example 49:
N—(Ethoxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—phenyloxyamidino—3-picolyl]amide

This compound was prepared analogously to Example 11 by esterification of N—(hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—phenyloxyamidino—3-picolyl]amide (Ex. 48) with ethanol in a 4N solution of hydrogen chloride in dioxane.
FAB-MS ($M+H^+$): 577

Example 50:
N—(Hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—isopentyloxyamidino—3-picolyl]amide

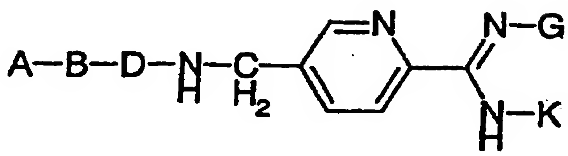
This compound was prepared analogously to Example 43, the product t—BuO_2C—CH_2—(Boc)—(D)—Cha—Pyr—NH—3—(6—C=NH(SCH_3))—pico x HI obtained in 41c) being reacted with O-isopentylhydroxylamine hydrochloride in the presence of six equivalents of diisopropylethylamine. The removal of the Boc protective group and the hydrolysis of the tert-butyl ester was carried out using a solution of hydrogen chloride in diethyl ether.
FAB-MS (M+H+): 543

Example 51:
N—(Ethoxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6-isopentyloxyamidino—3-picolyl]amide

This compound was prepared analogously to Example 11 by esterification of N—(hydroxycarbonylmethylene)—(D)—cyclohexylalanyl—3,4—dehydroprolyl—[6—isopentyloxyamidino—3-picolyl]—amide (Ex. 50) with ethanol in a 4N solution of hydrogen chloride in dioxane.
FAB-MS ($M+H^+$): 571

We claim:

1. A compound of the formula I



(I)

in which A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $HO-CH_2-CH_2-$, $R^2R^3N(O)C-CH_2-$, $R^2R^3N-O-CO-CH_2-$, $R^2N(OH)-CO-CH_2-$, where R^2 and R^3 independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_3-alkyl, or benzyl, or R^2 and R^3 together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ (q = 1-4), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where a phenyl ring can be fused to the cycloalkyl ring, pyranyl-, piperidinyl-, aryl- or phenyl-C_1-C_3-alkyl-, where except for H all radicals mentioned can optionally carry up to 4 identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals, or

R^1 is (2-oxo-1,3-dioxolen-4-yl)methyl-, which can be substituted in the 5-position by C_1-C_{16}-alkyl or aryl,

or

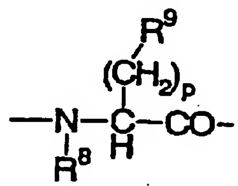
R^1 is: $R^4-C(O)O-C(R^5)_2-$, $R^4-C(O)NR^2-C(R^5)_2-$, where R^4 can be C_1-C_4-alkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, C_3-C_8-cycloalkyl-, C_1-C_4-alkyloxy-, C_3-C_8-cycloalkyl-C_1-C_3-alkyloxy-, C_3-C_8-cycloalkyloxy-, aryl- or phenyl-C_1-C_6-alkyl-, the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, and R^2 has the meaning indicated above, $R^6OOC-C_1-C_6$-alkyl, $R^6R^7N(O)C-C_1-C_6$-alkyl-, $R^6R^7N-C_2-C_6$-alkyl-, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl, or

if R^1 is $R^6R^7N(O)C$—C_1—C_6—alkyl—, R^6 and R^7 together form a C_4-C_6-alkylene chain,

or A is:

C_1-C_4-alkyl-SO_2-$(CH_2)_{2-6}$- , HO_3S-$(CH_2)_{4-6}$-, 5-tetrazolyl-$(CH_2)_{1-6}$-, C_1-C_4-alkyl-O-$(CH_2)_{2-6}$-, R^2R^3N-$(CH_2)_{2-6}$-, R^2S-$(CH_2)_{2-6}$-, $R^2R^3NSO_2$-$(CH_2)_{2-6}$-, HO-$(CH_2)_{2-6}$-,

B is

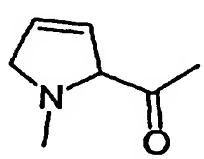
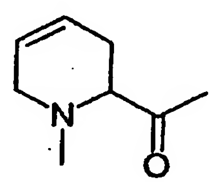


p is 0,1,2

R^8 is H—, $R^{10}OOC$- where R^{10}= C_{1-16}—alkyl—, phenyl—, C_3—C_8—cycloalkyl-, phenyl-C_1-C_4-alkyl-, $R^{11}C(O)$-O-CH_2-, $R^{11}C(O)$-O-$CH(CH_3)$-, where R^{11} can be C_1-C_4-alkyl-, phenyl-, benzyl-, C_3—C_8—cycloalkyl- or cyclohexyl-CH_2-,

R^9 is C_{3-8}—cycloalkyl—, which can carry up to four identical or different C_{1-4}—alkyl radicals,

D is:

 (II)  (III)

G is: -H, -OH, -OR^{12},
in which
R^{12} is: -C_{1-8}—alkyl, -C_3—C_8—cycloalkyl, -C_1-C_3-alkyl-C_3-C_8-cycloalkyl, -aryl or -C_1-C_6-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals,

K is: H,
or G and K together form a —C(O)O-group,

their configurational isomers, tautomers and their salts with physiologically tolerable acids,

where the following applies:

(i)

if D = (II) or (III) and G = $-H$, $-OH$, $-OR^{12}$,

in which

R^{12} is: $-C_1-C_8$-alkyl, $-C_1-C_3$-alkyl-C_3-C_8-cycloalkyl, -aryl or $-C_1-C_6$-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals

K is: H,

or G and K together form a $-C(O)O$-group, then A and B have the following meanings:

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $HO-CH_2-CH_2-$, $R^{2a}R^{3a}N(O)C-CH_2-$, $R^2R^3N-O-CO-CH_2-$, $R^2N(OH)-CO-CH_2-$, where R^2 and R^3 independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl or R^2 and R^3 together form a C_4-C_6-alkylene chain, R^{2a} is equal to H and R^{3a} is C_5-C_8-alkyl, C_3-C_8-cycloalkyl or benzyl;

in which

R^1 is: C_5-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where the phenyl ring can be fused to the cycloalkyl ring, pyranyl-, piperidinyl-, or aryl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals, or
R^1 is (2-oxo-1,3-dioxolen-4-yl)methyl which can be substituted in the 5-position by C_1-C_{16}-alkyl or aryl,

or

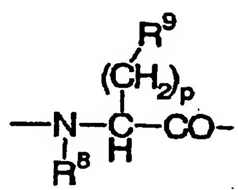
R^1 is: $R^4-C(O)O-C(R^5)_2-$, $R^4-C(O)NR^2-C(R^5)_2-$, where R^4 can be C_1-C_4-alkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, C_3-C_8-cycloalkyl-, C_1-C_4-alkyloxy-, C_3-C_8-cycloalkyl-C_1-C_3-alkyloxy-, C_3-C_8-cycloalkyloxy-, aryl- or phenyl-C_1-C_6-alkyl-, the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, and R^2 has the meaning indicated above,

$R^6OOC-C_1-C_6$-alkyl-, $R^6R^7N(O)C-C_1-C_6$-alkyl-, $R^6R^7N-C_2-C_6$-alkyl-, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl, or if R^1 is $R^6R^7N(O)C-C_1-C_6$-alkyl-, R^6 and R^7 together form a C_4-C_6-alkylene chain,

or A is :

C_1-C_4-alkyl-$SO_2-(CH_2)_{2-6}$- , $HO_3S-(CH_2)_{4-6}$-, 5-tetrazolyl-$(CH_2)_{1-6}$-, C_1-C_4-alkyl-O-$(CH_2)_{2-6}$-, $R^2R^3N-(CH_2)_{2-6}$-, $R^2S-(CH_2)_{2-6}$-, $R^2R^3NSO_2-(CH_2)_{2-6}$-, $HO-(CH_2)_{2-6}$-,

B is



p is 0,1,2

R^8 is H-, $R^{10}OOC$- where R^{10}= C_{1-16}-alkyl-, phenyl-, C_3-C_8-cycloalkyl-, phenyl-C_1-C_4-alkyl-, $R^{11}C(O)-O-CH_2$-, $R^{11}C(O)-O-CH(CH_3)$-, where R^{11} can be C_1-C_4-alkyl-, phenyl-, benzyl-, C_3-C_8-cycloalkyl- or cyclohexyl-CH_2-,

R^9 is C_{3-8}-cycloalkyl-, which can carry up to four identical or different C_{1-4}-alkyl radicals,

or

(ii)

if D = (II) or (III) and G = $-OR^{12}$,

in which

R^{12} is: $-C_5-C_8$-alkyl, $-C_3-C_8$-cycloalkyl, $-C_1-C_3$-alkyl-C_3-C_8-cycloalkyl, -aryl or $-C_1-C_6$-alkylphenyl, which can optionally carry up to three C_1-C_4-alkyl, CF_3, F, Cl, or C_1-C_4-alkoxy radicals,

K is: H,

or G and K together form a -C(O)O-group, then A and B have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^{2a}R^{3a}N(O)C-CH_2-$, where R^{2a} and R^{3a} independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl or R^{2a} and R^{3a} together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_4-alkyl- or phenyl-C_1-C_4-alkyl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from C_1-C_4-alkyl, CF_3, F, Cl, NO_2, HO or C_1-C_4-alkoxy radicals,

B, p and R^8, R^9, R^{10} and R^{11} have the meaning indicated in i).

2. A compound of the formula I as claimed in claim 1 in i), in which A, B, D, G and K have the following meanings:

A is: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$,

in which

R^1 is: C_5-C_{16}-alkyl-, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_{10}-tricycloalkyl-, C_{10}-tricycloalkyl-CH_2-, C_3-C_8-cycloalkyl-, C_3-C_8-cycloalkyl-C_1-C_3-alkyl-, where a phenyl ring can be fused to the cycloalkyl ring, pyranyl-, piperidinyl-, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3, CF_3, F, Cl, HO or methoxy radicals, or

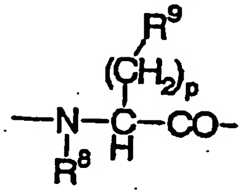
R^1 is (2-oxo-1,3-dioxolen-4-yl)methyl-, which can be substituted in the 5-position by C_1-C_3-alkyl or aryl,

or

R^1 is: $R^4-C(O)O-C(R^5)_2-$, where R^4 C_1-C_4-alkyl-, C_3-C_8-cycloalkyl-, C_1-C_4-alkyloxy-, C_3-C_8-cycloalkyl-C_1-C_3-alkyloxy-, C_3-C_8-cycloalkyloxy-, or aryl- the two radicals R^5 independently of one another are H, CH_3 or C_2H_5, $R^6OOC-C_1-C_6$-alkyl-, $R^6R^7N(O)C-C_1-C_6$-alkyl-, $R^6R^7N-C_2-C_6$-alkyl-, and in which R^6 and R^7 independently of one another are H or C_1-C_6-alkyl or,

if R^1 is $R^6R^7N(O)C-C_1-C_6$-alkyl-, R^6 and R^7 together form a C_4-C_6-alkylene chain,

B is



p is 0,1

R^8 is H–, R^{10}OOC- and R^{10}= C_{1-8}–alkyl–, phenyl–, C_3–C_8–cycloalkyl-, phenyl-C_1-C_4-alkyl-,

R^9 is C_{3-8}–cycloalkyl–, which can carry up to four identical or different C_{1-4}–alkyl radicals,

D = (II)

and G = -H, –OH, -O-C_1-C_8–alkyl,

K is: H

or G and K together form a –C(O)O-group.

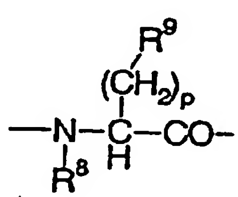
3. A compound of the formula I as claimed in claim 1 in ii), in which A, B, D, G and K have the following meanings:

A is: R^1OOC–CH_2-, R^1OOC–CH_2–CH_2-, R^1OOC–CH(CH_3)-, $R^{2a}R^{3a}$N(O)C-CH_2-, where R^{2a} and R^{3a} independently of one another are H, C_1-C_6-alkyl, C_3-C_8-cycloalkyl or benzyl, or R^{2a} and R^{3a} together form a C_4-C_6-alkylene chain,

in which

R^1 is: H-, C_1-C_4-alkyl- or phenyl–C_1–C_4–alkyl–, where except for H all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3, CF_3, F, Cl, HO or methoxy radicals,

B is



p is 0,1

R^8 is H–, $R^{10}OOC$– and R^{10}= C_{1-16}–alkyl–, phenyl–, C_3–C_8–cycloalkyl–, benzyl–,

and R^9 has the meaning indicated in ii)

D = (II)

G = $-OR^{12}$,

in which

R^{12} is: $-C_5$–C_8–alkyl, $-C_3$–C_8–cycloalkyl, $-C_1$–C_3-alkyl-C_3–C_8-cycloalkyl, -aryl or $-C_1$–C_6-alkylphenyl, which can optionally carry up to three CH_3–, CF_3–, F–, Cl–, or methoxy radicals,

K is: H,

or G and K together form a –C(O)O– group.

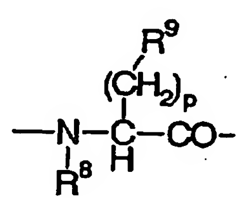
4. A compound of the formula I as claimed in claim 1, in which A, B, D, G and K have the following meanings:

A is: R^1OOC–CH_2–, R^1OOC–CH_2–CH_2–, R^1OOC–$CH(CH_3)$–,

in which

R^1 is: C_5–C_{10}–alkyl–, C_4–C_7–cycloalkyl–, C_4–C_7–cycloalkyl-CH_2–, where all radicals mentioned can optionally carry up to four identical or different radicals selected from CH_3– and methoxy–,

B is

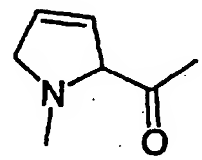


p is 0,1,

R^8 is H–,

R^9 is C_{4-7}–cycloalkyl–, which can carry up to four identical or different methyl or ethyl radicals

D is:



(II)

G is: -OH,
K is: H.

5. A compound, its configurational isomers, tautomers and its salts with physiologically tolerable acids, selected from the group:

$HOOC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$H_3CO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$EtO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$nPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$nBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$iBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$tBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$BnO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OH)]-pico$
$HOOC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$EtO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$nPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$iPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$nBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$iBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$tBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OH)]-pico$
$H_3CO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$EtO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$nPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$nBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$iBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$tBuO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(H)]-pico$
$H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$EtO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$nPrO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$nBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$iBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$tBuO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(H)]-pico$
$HOOC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(O-allyl)]-pico$
$H_3CO-OC-CH_2-(D)-Chg-Pyr-NH-3-[6-am-(OCH_3)]-pico$

iPrO-OC-CH_2-(D)-Cha-Pyr-NH-3-[6-am-(OCH_3)]-pico

6. A drug comprising, in addition to customary vehicles and excipients, compounds of the general formula I as claimed in any one of claims 1 to 5.

7. The use of compounds of the general formula I as claimed in any one of claims 1 to 5 for the production of drugs for the therapy and prophylaxis of thrombin-dependent thromboembolic events.

8. The use of compounds of the general formula I as claimed in any one of claims 1 to 5 for the production of drugs for the therapy and prophylaxis of

- disorders whose pathological mechanism is based directly or indirectly on the proteolytic action of thrombin,
- disorders whose pathological mechanism is based on the thrombin-dependent activation of receptors and signal transduction,
- disorders which are accompanied by stimulation or inhibition of gene expression in body cells,
- disorders which are based on the mitogenic action of thrombin,
- disorders which are based on a thrombin-dependent contractility and permeability change in epithelial cells,
- thrombin-dependent, thromboembolic events,
- disseminated intravasal coagulation (DIC),
- reocclusion and for the reduction of the reperfusion time in the case of comedication with thrombolytics,
- the occurrence of earlier reocclusion and later restenosis after PTCA,
- the thrombin-dependent proliferation of smooth muscle cells,
- the accumulation of active thrombin in the CNS,

– tumor growth and against the adhesion and metastasis of tumor cells.

9. The use of the compounds of the general formula I (as claimed in any on of claims 1 to 5 as prodrugs for the production of a drug for oral or parenteral administration.

10. The use of compounds of the general formula I as claimed in any one of claims 1 to 5 for the production of drugs having improved absorption in the gastrointestinal tract or a flattening of the amplitude of the plasma concentration time profile over the dose range or an increase in the duration of action of the active compound, comparison in each case being made with the pharmacologically active compounds.